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BLOOD VOLUME AND ITS REGULATION

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Much of our information with regard to the blood volume and its regulation has come to us through efforts that have been made to develop methods, and often this information is colored by the individual method through which it has been derived. This relation of information to method has determined the manner of treating the subject matter of this review. The various methods are grouped as far as possible according to their underlying principles and each of the more important groups with its related problems is examined critically in turn. Subsequently the more general phases of the subject are reviewed in relation to the problem as a whole and in relation to certain specific problems. The older literature is referred to only in so far as has seemed necessary in order to present the basis of methods and problems of current interest. More complete reviews of methods will be found in articles by Hayem (1), Plesch (2) and von Behring (3).

Blood volume methods may be divided into two groups according as they are designed for the determination of the absolute or of the relative blood volume. The methods of the first group are divided by Hayem (1) into two categories according as the blood volume is determined by direct or by indirect means.

DIRECT METHODS

The direct methods seek to determine the total blood volume by actually collecting all of the blood in the body by hemorrhage, by washing out the circulation, and by leaching the macerated tissues. The blood volume is then estimated by determining the degree of dilution of the combined blood and washings through comparison of the concentration of some one of its constituents with the concentration of that constituent in an undiluted sample of the normal blood of the same animal.

This principle was first employed by Lehmann and Ed. Weber in 1850 (4). They collected the blood of two executed criminals and then washed out the circulation with water.

Welcker's method. The method as modified by Welcker (5), (6) is more or less familiar to all who have an acquaintance with physiology. Welcker not alone washed out the vessels with water but also leached out the macerated tissues, and used the hemoglobin as a means of determining colorimetrically the relative concentration of the original blood and washings. In the case of small animals the body was merely ground up and extracted after drawing a sample of blood. Malassez (7) washed out the vessels and leached the tissues with an "artificial serum" containing gum arabic, sodium chloride and sodium sulphate, and made the comparison by counting the red cells. He took pains to prevent coagulation of the drawn blood.

Certain sources of error and difficulties inherent in the method early came to be recognized. Aside from defects in colorimetric technique, a subject which does not directly concern us here, these have been found to consist *a*, of the presence in the tissue extracts of muscle hemoglobin as well as hemoglobin of the blood; *b*, of the difficulty in matching the color of the tissue extract and that of the blood due to turbidity of the former; *c*, of the loss of hemoglobin due to efforts to clear the extract of its turbidity; and *d*, of the loss of hemoglobin due to both intra- and extravascular clotting.

It was realized even by Welcker (6) that the washout method would be decidedly improved if all of the blood could be obtained merely by washing out the circulation. One of the difficulties in the way of accomplishing this is the gradual slowing up of the perfusion due very largely to the development of edematous swelling of the tissues, but partly, possibly, to the formation of intravascular clots (8).

Suter and Jaquet (9) essayed to minimize the former difficulty, and also to obtain a better penetration of the circulation, by flushing out with fluid driven by a pulsating instead of a constant pressure. In the rabbit they alternately drew blood from the carotid artery of one side and injected warm 1.0 per cent sodium chloride into the jugular vein of the opposite side. They thus found it possible to inject into the circulation as much as 500 cc. of fluid before the heart stopped. Then the thorax was opened and artificial perfusion of the circulation begun with sodium chloride solution driven by a pulsating pressure. At the same time the animal was vigorously massaged. Extraction of the tissues after the washings became clear yielded at most 1.0 to 1.8 per

cent of the total hemoglobin. Separate extraction of the pale and the red muscle indicated that the largest part of this residual coloring matter came from the myohemoglobin rather than the blood; they consequently discarded leaching of the tissues, since they feel that the turbidity of tissue extracts introduces into the colorimetric determinations a larger error than does any incompleteness of the washing out of the vessels as practiced by them.

Dreyer and Ray (10), also working with the rabbit, substitute oxygenated Locke's solution for the sodium chloride solution and interrupt the inflow 10 to 15 seconds in each minute. Under these circumstances the heart continues to beat 4 to 5 hours, and until the washings become colorless or nearly so; but they continue the washing (now under a constant pressure) for from 1 to 6 hours longer. As the carcass, when extracted, yields 1 per cent or less of hemoglobin, they, likewise, abandon subsequent extraction of the tissues. The difficulty in reaching all parts of the circulation by perfusion and the necessity of using passive movements and massage in order to secure a maximum yield are illustrated by the observation that at a time when the perfusion fluid is coming away clear, artificial respiration may cause it to become bloody again. The blood and washings are received into vessels containing hirudin in order to prevent clotting, which in their experience removes hemoglobin. The precautions taken by Suter and Jaquet to prevent clotting do not seem to have been entirely effective.

The largest number of blood volume determinations in the rabbit in recent years has been made by Boycott and by Douglas (11), (12), (13) and by Abderhalden (14). Boycott and Douglas used a technique that differed very slightly from that originally described by Welcker. The animals were bled to death into oxalate solution and the circulation then immediately washed out, under a constant pressure, with 3 to 4 liters of an 0.8 per cent sodium chloride solution containing 1.0 per cent of sodium citrate, with the assistance of massage. In a few experiments the completeness of the washing was controlled by subsequently macerating and extracting of the tissues. It was found that perfusion obtained 93 per cent of the total volume of blood, and that the long bones retained 3 per cent of the total. Abderhalden (14) used for the determination of the blood volume Bunge's modification of the Welcker method. After taking a sample of blood the animal is killed. The skin and the gastro-intestinal canal are then removed by a method which, according to Abderhalden, carries away at most a negligible quantity of blood, and the remaining tissues are ground up and repeatedly macerated and

extracted. Inspection of our table listing results obtained by all of the more important methods does not give any evidence that the seemingly better methods as applied to the rabbit yield the larger blood volumes.

According to Gscheidlen (15), dog's muscle may contain as much as 4 to 5 per cent of the total hemoglobin. In the case of this animal, therefore, it is even more important than in the rabbit to find a way of dispensing with tissue extraction. Efforts in this direction, though, have been even less successful than in the rabbit. Müller (15) used most of the devices that have led to fairly complete yields in the case of the latter animal. In addition, in order to prevent intravascular clotting, he injects at one stage of the process a 0.9 per cent solution of sodium chloride containing 1 per cent of ammonium oxalate. Nevertheless, subsequent extraction of the macerated carcass (17) discloses from 8 to 16 per cent of the total hemoglobin, 8 to 13 per cent being in the bones alone, held there, Müller believes, in some way by the structure of the tissue. Plesch (2), using essentially the same technique, finds 64.8 per cent of the hemoglobin in the washings, 26.2 per cent in the extract from the macerated soft parts and 8.2 per cent in the bones. (Plesch's figures do not total 100.) Gscheidlen (15) recommended separate extraction of the muscle so that an allowance might be made for its peculiar hemoglobin. But Müller knows of no technique, applicable to the dog, that will circumvent the myohemoglobin without at the same time withdrawing from estimation a considerably larger amount of actual blood pigment. Neither he nor Plesch in their experiments make any allowance for such myohemoglobin as may be extracted.

Brodin, Richet and Saint-Girons (18), who alone dispense with extraction of the tissues, have determined the blood volume in a very large series of dogs. In our opinion, though, there are reasons for doubting the thoroughness of their method. They first bleed the animals, then inject 250 to 300 cc. of a 6.0 per cent solution of sodium citrate and finally wash out the circulation with 30 to 40 liters of a 5.0 per cent solution of Na_2SO_4 under a *constant* pressure. They do not use massage. Indeed, they seem to assume that they are doing all that is necessary to obtain a complete yield of blood, for they do not subsequently macerate and extract the tissues, nor do they say anything with regard to their blood content upon completion of the perfusion. They feel that their technique is better than any previously employed because steps are taken to avoid intravascular clotting and hemolysis with consequent loss of hemoglobin, apparently without realizing that some previous investigators have provided against these possible sources of error,

and that essentially the same technique in the hands of others leaves in the body of the dog between 8 and 26 per cent of the blood. Their washout method is essentially that of Malassez (7), excepting that it omits subsequent extraction of the tissues. It is supposed to preserve the red corpuscles intact, and the concentration comparisons are made by counting the red cells in the Malassez hematinometer. The French observers, however, present no evidence indicating absence of disintegration or of clumping of red cells; furthermore the constancy of the Malassez instrument has been questioned by Alferow (19). The results obtained by them are in general quite low (see table), occasionally below 5 per cent of the body weight (see also Malassez, 20). That their results are low they realize, but they attribute this to the large size of their animals. It is scarcely possible to reconcile such figures, though, with the fact that dogs can survive an acute hemorrhage of the same (21), or even larger amounts (22); they probably account for their observation that dogs may survive as long as a half-hour a hemorrhage that leaves only 2.8 to 6.7 per cent of their red cells (!) and 25 per cent of their blood (compare with Rous and Wilson, 23).

So far as we have been able to ascertain crucial tests of the accuracy of the direct method are lacking. The method should be controlled by injecting into the circulation at a time the washings are coming away almost colorless, but while the heart is still beating, blood containing a known amount of hemoglobin, allowing this to circulate in the animal for a few moments, and then determining whether the injected hemoglobin can be recovered quantitatively by again washing out the circulation. The same sort of a test should be applied to tissue that has been macerated and extracted until the extract becomes colorless. In this connection Dreyer and Ray (10) state that a turbid fluid cleared by centrifugation may lose even up to 40 to 45 per cent of its original hemoglobin. They are inclined to believe that the low results some have gotten by the extraction method (Ranke, for example, 24) are due to their efforts to clear a turbid extract.

INDIRECT METHODS

The idea of determining the blood volume indirectly seems to have originated with Valentin (25). By way of illustrating the general principle that forms the basis of almost all of the methods since developed, his method may be briefly described. A sample of blood, b, is drawn and the percentage of solids, p, in it is determined. Then a known volume, w, of distilled water is injected intravenously. After a lapse

of a period of time which is supposed to suffice for thorough mixture of the injected water with the blood, but presumably before appreciable amounts have left the circulation, the percentage of solids, q, in the blood is again determined. Then the blood volume, v', at the time of the injection is to the original percentage of solids as the amount of water injected is to the degree of dilution of the blood, which is given by the difference $p - q$, whence

$$v' = \frac{p\,w}{p - q}$$

The original blood volume, v, is obtained by adding to this the amount of the sample, whence

$$v = \frac{p\,w}{p - v} + b$$

The objection to the use of distilled water for intravenous injection soon led to the use of salt solution in its stead. Sander and Kronecker (26) substituted for blood an equal volume of sodium chloride solution and determined the degree to which it diluted the hemoglobin. They did not consider the method as entirely satisfactory. Sherrington and Copeman (27) diluted the blood with 0.75 per cent sodium chloride solution. In the case of the rabbit they injected an amount of the solution equal to about one-third of the blood volume in the space of 15 seconds, and determined the degree of dilution 30 seconds later, using the specific gravity of the blood as an index. This time interval was deemed sufficient to effect complete mixture with the blood because it allowed 5 to 6 circuits of the body, and because the blood drawn was of a lower specific gravity 30 and 45 seconds after completion of the injection than it was either before or after that time interval had elapsed. They found, though, that even in that short period some of the sodium chloride solution (about 7 per cent) escaped from the circulation. Sherrington and Copeman do not claim any high degree of accuracy for the method, and their estimated values show a very wide range of variation. Kottmann (28) applied the sodium chloride dilution method to man. He injects about 3.5 cc. of strictly isotonic solution per kilo of body weight. The degree to which the blood is diluted is determined by means of a special hematocrit. He seems to be of the opinion that the injected solution mixes only with the blood that is in active circulation, and is convinced that owing to the relatively small amount of solution injected practically none leaves the circulation during the 10-

minute combined injection and mixing period. Plesch (2), in man, injects a somewhat larger quantity of sodium chloride solution (5 cc. per kilo of body weight) in from 2 to 9 minutes and then draws samples of blood immediately and at 2 minute intervals thereafter. The hemoglobin concentrations are matched in the Plesch colorimeter. It is thus found that for a while, usually for 2 to 3 minutes, the blood dilutes and then begins to concentrate. Plesch's figures show many variations from this type (see curves *7* and *8*); indeed, in one half of his cases the first reading is the lowest. He has made comparative estimations in one and the same animal first by this method, and immediately after by the washout method. The results agreed practically perfectly. He also believes that only inconsiderable amounts of the injected solution could leave the circulation during the injection and post-injection periods. de Crinis (29) uses essentially the same technique but determines the grade of dilution of the plasma by means of the refractometer after making a fixed correction determined by the dilution of highly refractive substances other than proteins, such as urea and glucose. As these same substances enter diluted blood very rapidly, especially urea (30), it is possible that his correction factor is too large.

The accuracy of the sodium chloride dilution methods, aside from technical errors, depends almost entirely upon two conditions, namely, *a*, that the time allowed for mixture with the blood is sufficient, and *b*, that negligible amounts of the solution escape from the circulation during the injection and post-injection periods. At this time only the specific question of the *rate of disappearance of the sodium chloride* from the circulation will be considered. Practically all of the advocates of this method of determining the blood volume cite Cohnstein and Zuntz (31) as having demonstrated that injected isotonic sodium chloride solution leaves the circulation very slowly. These investigators injected into rabbits of known weight a known volume of solution and found, after dilution of the blood, that the number of red cells per unit volume equalled, within the limit of error, the number derived by calculation from the unwarranted assumption that the blood of the rabbit equals $\frac{1}{14}$ of the body weight. Had they employed the value $\frac{1}{20}$, which is more nearly correct, the calculation would have disclosed a rapid disappearance of the solution. Most advocates of this method admit that sodium chloride solutions can escape rapidly from the circulation, but, overlooking the results of Sherrington and Copeman (27), they argue that this occurs only when very much larger amounts are injected than those they use. It is possible, however, by selecting

the appropriate section of a curve of disappearance of large doses of sodium chloride solution, such even as those given by Smith and Mendel in the rabbit (32), to ascertain the rate of disappearance of any smaller dose. It is thus found (see curve *9*) that in the course of 4 to 5 minutes, the time usually allowed to elapse after injection in man, about *25 to 30* per cent of the solution injected disappears, but in the rabbit. This does not take into account such disappearance as may be occurring during the injection period. Plesch (2) lays great stress upon the fact that after injection the blood for a time dilutes and then *very slowly* concentrates; this behavior he believes is indicative of slow disappearance of the solution from the circulation; but, as will be seen, other explanations are possible.

Some other dilution methods. Loewy (33), in man, injects isotonic glucose (500 cc.) and uses the resulting dilution of the sodium chloride of the blood as an index to the blood volume. The method has been severely criticised by Boenheim and Fischer (34), mainly upon the basis of the method (Bang's micro method) used by Loewy for determining the sodium chloride. Other serious objections to the method are that injected water does not remain in the circulation any longer than does isotonic sodium chloride (27), and that sodium chloride immediately begins to enter the blood stream from the tissues. The slow rate of injection he uses (10 minutes), to say nothing of the post-injection period of 5 to 10 minutes, allows ample opportunity for these interchanges to occur. A somewhat similar method, described by Deycke Pascha (35), who employs changes in protein concentration as the index to dilution, also seems not to be without objection. Malassez in 1874 (7) suggested the use of serum as a diluent. This idea would probably prove useful for the determination of the blood volume in animals for which compatible serum is readily obtainable, for serum has the advantage over most of the fluids available for this purpose that it leaves the circulation relatively slowly. Possibly, though, its constricting action (36), which Rous and Wilson (23) believe has been over emphasized, may alter the blood volume. Robertson and Bock (37) used Bayliss' solution (6 per cent gum acacia in 0.9 per cent sodium chloride) as the diluent and the hemoglobin as the index to the dilution. This procedure, on account of the slow rate with which gum solutions leave the circulation (32), (38), (39), (40), (41, etc.), must be very much superior to the other injection methods thus far considered with the possible exception of Malassez's. Robertson and Bock had an opportunity to compare in one and the same patient the reading made by

this method and by the vital red method and obtained with the latter a reading higher by 3 per cent. Curiously enough, they charge the error against the account of the gum solution.

Replacement methods. In order to avoid an increase in arterial pressure with possible consequences upon the blood volume, Malassez (7) suggested that the animal be first bled and then transfused with an equal amount of serum. Nelson (42) has made practical use of the method. The dilution of the blood was determined a *half-hour* after the injection, only. If a relative as well as an absolute reduction in red cells is without effect upon the blood volume, and if serum (or plasma) so injected actually remains in the circulation in undiminished amount for the period mentioned above, and does not alter the blood volume through its constrictor action, this method would be without a peer. In two rabbits Nelson determined the blood volume, first by this method and then by the washout method. The former method gave values (converted into mass) of 6.4 and 6.1, the latter of 5.7 and 6.4 per cent of the body weight, respectively. In each of two dogs a volume (converted into mass) of 7.1 per cent of the body weight was found. The former results seem high, the latter low.

Harris (43) has recently described a method which he believes yields the nearest approach hitherto attained to the absolute value of the blood volume. It consists in bleeding the animal while transfusing into a vein at the same rate Bayliss' gum-saline fluid. It is thus possible, Harris says, to remove quite $\frac{9}{10}$ of the hemoglobin before the animal dies. Just before this point is reached the process is stopped, and after allowing 3 to 5 minutes for thorough mixing of the remaining blood with the known volume of injected gum-saline, a sample of blood is drawn. The blood volume is calculated by introducing into his formula, which space prevents our developing, values obtained through hemoglobin readings. Harris presents no convincing proofs of the accuracy of the method. It seems possible that the extreme asphyxia to which the tissues are subjected by the method might lead to impairment of the walls of the capillaries and transudation of fluid.

Hemorrhage method. Vierordt (44) based a formula which gives the blood volume upon the assumption that the reduction in the number of red cells that develops during the first few hours after hemorrhage is entirely relative and due to replacement of the fluid drawn. He did not claim for the method any great degree of accuracy. Dreyer and Ray (10) have recently (1910) made an attempt to perfect the method. In the rabbit they find that after a hemorrhage removing about 20 to

25 per cent of the estimated total blood volume, the percentage of hemoglobin falls for about 24 to 48 hours and then remains constant for about 24 hours before it begins to increase. They believe that during this constant period the blood volume is at its original normal level. In support of this contention they point to their series of 22 blood volume estimations, 10 by the present method, the remainder by their modification of the washout method, in which the agreement is so close that the estimations by the two methods cannot be distinguished from each other. Upon the whole the figures obtained from the literature, as recalculated by Boycott and Douglas (12), indicate that the lowest point reached by the hemoglobin after hemorrhage, does correspond with the restoration of the blood volume. There are, however, exceptions to this rule which indicate the necessity of always carefully controlling the method. Thus Boycott and Douglas (12) and Douglas (45) in the rabbit and Keith (46) in man find that at this time the blood volume exceeds the normal; Whipple and colleagues (47) using vital red, that it is less than normal, though certain features of their experiments are inexplicable. Even more serious, perhaps, is the number of factors which seem to affect the rate of regeneration. Amongst these are the extent of the hemorrhage (37), the amount of water (12), (37) and the kind of food (48), (49), (50), (51), (52) ingested, and the effect of light and darkness (48). The fact that the method can be employed only in animals that have not been bled before, also is indicative of the unstable position of the equilibrium point of blood regeneration.

The carbon monoxide method. Gréhant and Quinquaud in 1882 (53), (54) essayed to determine the blood volume in the dog by adding to the air inhaled a measured volume of carbon monoxide, one short of the amount that produces symptoms of oxygen want, and then determining by gasometric methods the proportion of hemoglobin remaining combined with oxygen. Haldane and Smith (55) adapted the method to the determination of the blood volume in man and used for the determination of the carbon monoxide hemoglobin Haldane's carmine method which requires only a few drops of blood, but which in the hands of most investigators has proved unsatisfactory (56), (57), (58). Improved gasometric methods of determining the carbon monoxide were suggested by Oerum (48), (56) and by Zuntz and Plesch (58). The technique of all of these methods, though, is difficult and considerable practice is necessary to master it (2), (12), (59). More recently (1919) Van Slyke and Salvesen (60) have described what seems to be a simpler gasometric method which determines

the gas more quickly, more accurately and in smaller quantities of blood. Salvesen has used this method for the estimation of the blood volume in the rabbit and in man (61).

Haldane and Smith (55) considered as the only considerable source of error, aside from those of a technical nature, which are admittedly large (62), combination of the carbon monoxide with myohemoglobin, which, they estimated might cause not more than $\frac{1}{20}$ of the carbon monoxide to disappear from the blood stream. More recently (1910) Douglas (63) found that in man the percentage saturation of the blood with carbon monoxide may fall for as long as $16\frac{1}{2}$ minutes after terminating the inhalation, which itself lasts many minutes, and rightly, we believe (see page 194) uses for the calculation of the blood volume the reading obtained when the level of the carbon monoxide becomes constant. A number of tests have been made in an effort to ascertain the accuracy of the method. *a*, Douglas (63) determined his own blood volume every few days over a period of about 3 months and found the range limited to from 4360 to 5240 cc., the average being 4657 cc. *b*, Gréhant and Quinquaud (53) and Oerum (56) state that their methods indicate almost exactly the amount of blood removed by a hemorrhage. Boycott and Douglas (12) transfused or bled rabbits a measured amount and found that the method gave results consistent with the known change in volume. *c*, Douglas (11) and Boycott and Douglas (12) have compared the blood volume as determined in the same animal by the carbon monoxide method and then by the Welcker method and find the error, when all results are averaged, to be about nil; the range of error in individual trials, however, is wide and amounts to from +20 to −15 per cent. In a later paper, Boycott (13) collects the results of 36 determinations of the blood volume by the carbon monoxide method and 52 by the Welcker method in rabbits. The averages are 5.3 and 4.47 per cent, respectively. In other words, the Welcker method gave lower results than the carbon monoxide method. Boycott thinks this might be due to the myohemoglobin, which was not extracted by his washout method and which is determined by the carbon monoxide method; but, as will be seen, many of the injection methods, not influenced by myohemoglobin, also give higher results than the washout method. Dreyer and collaborators (10), (64), (65), (66) feel that the CO method gives inconstant results.

The table shows that with but one exception the method gives fairly consistent average figures in the case of the rabbit and of the dog. In the case of man, however, the values range between 4.78 per cent and

8.43 per cent. The fact that all those investigators (59), (61), (62), (63) who specifically state that more than a few minutes were allowed for mixture have gotten the higher results, and that those (61), (63) who used the longest time interval got the highest results, indicate that the differences are due to the time factor. The fact that Gréhant and Quinquaud, who allow 15 minutes to elapse, get only slightly higher results in the dog than did Plesch, and the fact that the time element makes no appreciable difference in the case of the rabbit, are not inconsistent with this point of view; for, on the basis of the pulmonary circulation time in the rabbit (3 seconds (67)), and in man (15 seconds), a 10-minute interval, for instance, in the case of the latter subject is the equivalent of a 50-minute interval in the former, a period undoubtedly sufficient for even distribution throughout the blood stream of the corpuscles carrying the inhaled gas.

Dilution of a foreign substance. A great variety of non-toxic, difficultly diffusible substances have been suggested for injection into the blood stream as a means of determining the blood volume; and a variety of methods of determining the degree to which these substances are diluted by the blood has been employed. Malassez in 1874 (7) recommended for the purpose the injection of the blood of an animal of the same species, but containing a different number of red cells, and determining the degree of dilution by means of red cell counts. In 1878 Quincke (68) employed the method for the estimation of the volume of blood in two cases of pernicious anemia by transfusing into patients whose red cells were reduced, the blood of normal subjects. Lindeman in 1918 (69) redescribed the method and made some determinations (70) in cases of pernicious anemia.[1] Abderhalden and Schmid (71) have recommended the injection of dextrin and its determination by means of the polariscope. As the dextrin begins (?) to disappear in $2\frac{1}{4}$ minutes and entirely disappears within 14 minutes, the method seems to be of very questionable value.

The exactness of the biological method of determining the antitoxin content of the blood, and its remarkable persistence in the blood after injection gave to von Behring the idea of employing it for the purpose of determining the blood volume (3). Curiously enough the injected antitoxin occurs in considerably lower concentration in blood from the right ventricle than in that taken from the carotic artery, which is

[1] Denny (139) determines the blood volume in pernicious anemia by the effect upon the oxygen capacity of the blood of the patient of injecting blood of a subject with a known normal oxygen capacity.

suggestive of its free passage into the lymph. The difference is sufficient to necessitate sampling distal to the portal system. The corpuscles, especially the white corpuscles (in leucemia), cause a slight diminution in the amount of antitoxin (72). On account of the danger of anaphylaxis determinations cannot be repeated. von Behring gives in very great detail the method of making determinations and concludes by saying that "if every precaution observed in von Behring's laboratory is not taken . . . . the number of sources of error is inconceivably large." The method has been used for the determination of the blood volume in man by Fries (73), by Matthes (89) and by Kammerer and Waldmann (72).

Schürer (74) injects a foreign serum and determines the grade of dilution by means of the precipitin reaction. The main advantage of the method is that the injected serum leaves the circulation very slowly: after a lapse of 3 hours it is still present in undiminished amount. The possibility that some disappears immediately does not seem to have been considered, nor that the constricting action of serum may affect the blood volume. Repeated determinations can be made with an error of about 10 per cent by using different kinds of foreign sera. It would, of course, be inadvisable to use it in man.

Meek and Gasser (41) estimate the blood volume by injecting 4 cc. of a 20 per cent solution of gum acacia per kilo of body weight and determining gravimetrically the amount of acacia in a known volume of blood 10 minutes later. In this time no appreciable diminution occurs in the amount in the circulation (see curve *6*). Some of the acacia disappears when it is added to blood; their method takes this into account. McQuarrie and Davis (75) inject a non-coagulable, highly refractive solution consisting of 20 to 25 per cent gum acacia and 10 to 20 per cent gelatin in 0.9 per cent sodium chloride and determine the change in the refractive index of the serum after precipitating the blood proteins. The mixing period they allow, 3 to 5 minutes, may not be sufficiently long for such a highly viscid solution. Furthermore, it is possible that the high colloidal osmotic tension their solution exerts may lead to an expansion of the blood volume (30), (76), (77), which Meek and Gasser (41) believe is not appreciable within 10 minutes after injection of a simple solution of 20 per cent acacia, and that the gelatin may rapidly disappear from the circulation (78). It is not surprising to find, therefore, that postponing the reading of the blood volume after the injection of the mixed solution increases the result quite appreciably.

Keith, Rowntree and Geraghty (79) succeeded in finding by means of appropriate tests a dye, vital red, which is non-toxic and escapes slowly from the blood stream, and in working out a practicable method for determining the blood volume with it, which has since been improved somewhat in certain respects by Hooper, Smith, Belt and Whipple (47). The dye is diffused in the plasma; therefore in addition to the colorimetric estimation of the dye in the plasma, the relative volume of the corpuscles must be determined by means of the hematocrit. All who have worked with vital red (43), (47), (79) state that when it is added to blood *in vitro* some disappearance occurs but that it is so close to the limit of the error of the colorimetric method that it is justifiable to disregard it. Inasmuch, however, as the average of the readings always is in the direction of disappearance of the dye and amounts to from 1 to 5 per cent, this attitude seems scarcely justifiable. Introduced into the circulation in usual amounts, disregarding for the present the behavior during the first few minutes, the dye disappears at a slow and constantly diminishing rate (see curves *2*, *3*, *4*).. This rate of disappearance is somewhat faster as determined by Harris than as determined by Whipple and colleagues, due possibly to the fact that Harris employed anesthetics whereas Whipple did not. Whipple states that no disappearance occurs during the second 2 minutes after injection. The curve we have constructed from his data (see p. 193) shows that this is not correct. The method has the advantage that it is simple to use and that repeated determinations at short intervals can be made on the same subject (80). The possibility of incomplete centrifugation of the red cells due to the employment of large tubes (81) seems to have been controlled (47), though Whipple and collaborators (47), (49) have recently encountered inconsistencies which they are not ready to discuss. There are no reasons for believing that their difficulties apply to the vital red method only. Dawson, Evans and Whipple (82), from amongst 60 dye substances, found 30 possessing the qualities essential for the estimation of the blood volume. Of these they prefer certain of the blue dyes to vital red, first because they happen to leave the circulation somewhat more slowly; second, because blues can be read more accurately and more rapidly; and third, because they do not obscure hemolysis. Harris (43) feels that Congo red is superior even to vital red as a dye for the determination of the blood volume, though he is still engaged in trying it out.

INTERPRETATION OF CONCENTRATION CURVES

Curve during the mixing period. In order to comprehend the processes determining the form of the concentration curves during the mixing period, it is necessary to think of the circulation as consisting not alone of the main systemic-pulmonic circuit, but of many subsidiary circuits inserted into it in parallel (83), all of very unequal lengths and resistances. To become mixed with the whole of the blood mass in such a circulation an injected substance must traverse the very slowest of the paths at least once. And until it is generally distributed, its concentration in the blood of the paths that have been threaded will be higher than the final concentration when mixing becomes complete. In other words, a curve based upon samples taken from a short path, the jugular vein for instance, presumably will at first rise above and then fall to the level determined by the even distribution of the injected substance. Without going into detail, it is obvious that the form of the early part of the concentration curve will depend upon the location in the circulation from which samples are taken, and that blood volume determinations based upon readings made before mixture has become intimate may, depending upon the region from which samples are taken, be high, or low, or, and then only by chance, correct.

Curve of disappearance. If a substance could be found for injection that did not leave the blood stream, its concentration curve, when mixing became complete, would run horizontally. As a matter of fact, however, all the substances we are dealing with must leave the blood stream more or less rapidly. If such a substance could be made to distribute itself instantaneously and evenly throughout the circulation, it is obvious that its rate of disappearance would have some direct relation to its concentration; that is to say, disappearance would be fastest at first.

Combination of curve of mixing and of disappearance. The conditions we have premised, however, are not attainable. There will always be an injection period, when the amount of the material in the circulation is increasing, and a mixing period outlasting it an unknown time. At what rate the substance will disappear during these periods, it it impossible to say. It is clear, however, that only that part of the concentration curve is indicative of the rate of disappearance which is inscribed after distribution has become uniform. It is barely possible that by means of backward exterpolation from the latter parts of the curve it might be possible to determine not alone the percentage

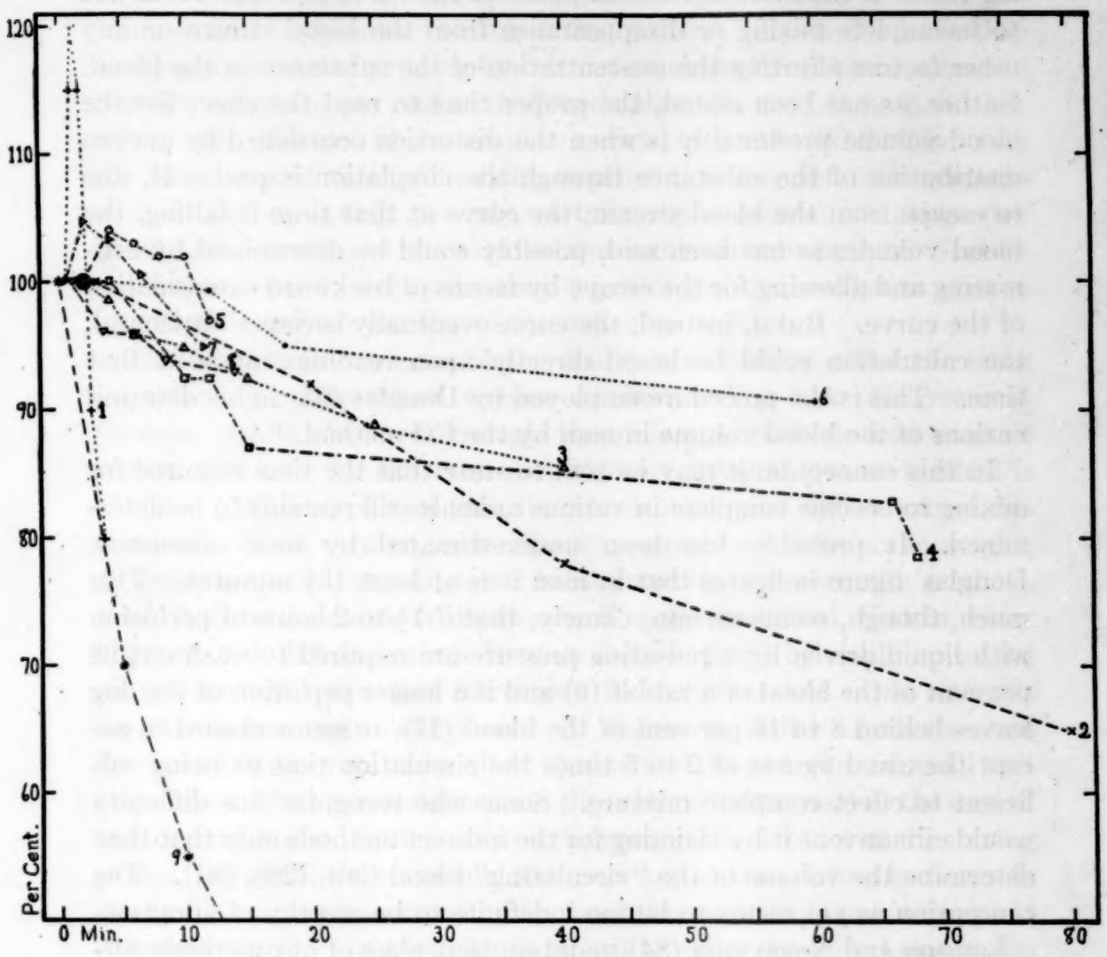
disappearance during the mixing period, but even the duration of the mixing period, and the concentration at the termination of the injection period.

Actual concentration curves. In the figure we have plotted concentration curves from such data as are available in the literature. Five are vital red curves. Two of them (*1* and *2*) are transcribed from Harris' curves *1* and *5* (43). Another (curve *3*) has been constructed from the elaborate data of Whipple and collaborators (82) (their table *3*), also derived from the dog, by assigning a value of 100 to each of the first of their 17 experiments, by expressing the subsequent readings in percentages of the first, and then using for each of the points on the curve the averages of the 17 readings belonging to it. This method of minimizing the experimental error makes this curve especially instructive. By a similar process curves *4* and *5* have been plotted from the only relevant data for the dog and for man, respectively, given by Rowntree and collaborators (79); curve *6* from data taken from Meek and Gasser showing the concentration changes of gum acacia in the blood of the dog (41), and curves *7* and *8* from Plesch's cases II and VI, respectively (2), to illustrate two types of concentration changes in the blood of man subsequent to the injection of sodium chloride solution.

Examination of these curves shows that with but one exception (curve *8*), the most rapid rate of decline fails to coincide with the start. Indeed, the start is protean in form, the most marked variation being exhibited by curve *1*. This may be due partly, as Harris believes (43), to the closeness of the points (half-minute intervals) determining it; though the fact that the samples were taken from a short path, the jugular vein, may have contributed. This curve Harris (43) uses to account for his finding that when readings in dogs are made 1½ minutes after injection (at the time his curve is at its crest) and 4 minutes after injection, the resulting figures indicating the blood volume are respectively 12 and 26 per cent above the figures obtained in the same animal by means of his replacement method. Parenthetically, it may be stated that upon the basis of comparative figures obtained by these two methods, Harris concludes that determinations by the vital red method are too high, but can be corrected by multiplying the 1½ minute and the 4-minute readings in the dog by the factors 0.90 and 0.75, respectively; and 4-minute readings in man by the factor 0.80. These values stand or fall with the correctness of Harris' replacement method.

Harris believes mixture is complete in the dog at the time, 80 seconds, the vital red reaches its maximum concentration. As this happens to

be about twice the total circulation time as deduced from Stewart's work (67), he infers that 2 to 2½ minutes would be the optimum time for the withdrawal of blood in human observations. Granting even that Harris is right, his deduction would bring us no closer to the possibility of accurately determining the blood volume because of the rapid-



Curve 1

ity of the fluctuations in the concentration of the injected substance at that time. Plesch (2) reads the blood volume (in man) at a similar stage after the injection of sodium chloride solution, i.e., when the dilution of the blood begins to give way to concentration; this, as has been seen, often occurs *immediately* after terminating the infusion, never more than 5 minutes later. And Sherrington and Copeman (27) for

the same reason sample the blood of the rabbit about 30 seconds after infusion.

Neither is there any assurance in the case of curves, such as some of Whipple's for vital red and Meek and Gasser's for gum acacia (curve *6*), which at first are practically horizontal or decline slightly, that a reading made in the more horizontal phase of the curve is free of error due to incomplete mixing or disappearance from the blood stream or any other factors affecting the concentration of the substance in the blood. Rather, as has been stated, the proper time to read the curve for the blood volume presumably is when the distortion occasioned by uneven distribution of the substance through the circulation is past. If, due to escape from the blood stream, the curve at that time is falling, the blood volume, as has been said, possibly could be determined by estimating and allowing for the escape by means of backward exterpolation of the curve. But if, instead, the curve eventually becomes horizontal, the calculation could be based directly upon readings made at that time. This is the procedure employed by Douglas (63) in his determinations of the blood volume in man by the CO method.

In this connection it may be well to state that the time required for mixing to become complete in various animals still remains to be determined. It probably has been underestimated by most observers. Douglas' figure indicates that in man it is at least 16½ minutes. This much, though, seems certain, namely, that if 1½ to 2 hours of perfusion with liquid driven by a pulsating pressure are required to wash out 98 per cent of the blood of a rabbit (9) and if a longer perfusion of the dog leaves behind 8 to 16 per cent of the blood (17), it seems absurd to accept the usual figures of 2 to 5 times the circulation time as being sufficient to effect complete mixture. Some who recognize this difficulty would circumvent it by claiming for the indirect methods only that they determine the volume of the "circulating" blood (26), (28), (84). The conception as yet seems to be too indefinite to be worthy of adoption.

Lamson and Nagayama (84) maintain that none of our methods suffice for the determination of the true total blood volume for the reason that blood is a suspension of corpuscles of constantly varying size (see Price-Jones, 85) in a fluid which is also undergoing variations in volume, and that the concentration of the corpuscles is not the same throughout the circulation. The questions here raised are considered later in connection with the subject of the relative blood volume. Here it may be said that these investigators do not present any new evidence indicating that variations of the kind mentioned are of sufficient magnitude to be

the cause of our difficulty in determining the *normal* blood volume (see p. 200); they merely assume that because vital red, which is diffused through the plasma, indicates a blood volume, in man, of 8.8 per cent and that because CO, which is carried by the erythrocytes, indicates a blood volume (in the hands of some investigators) of 5.5 per cent, therefore, the former determines the plasma volume, and the latter the volume of the corpuscles floating in that plasma. Upon this basis they develop a method of arriving by calculation at the "true blood volume." But why adopt 5.5 per cent as the blood volume by the CO method when others (62), (63) get figures as high as 8.4 per cent? While admitting the soundness of their underlying argument, it has yet to be demonstrated that, excepting, possibly, certain very abnormal conditions (see p. 202), the two types of blood volume methods necessarily give inconsistent results and, if they do, that the discrepancies are due to uneven distribution and uneven size of the red cells.

The table contains some of the results obtained by all of the more important absolute blood volume methods. The lack of agreement between results obtained through the different methods and even of results obtained by different investigators using the same method is obvious. While a part of this disagreement may be due to actual differences in blood volume, such as is determined by differences in weight, altitude, age, etc., etc., and a part to fundamental defects in the methods used, it nevertheless could be shown, if space permitted, that in many instances the differences can be materially reduced by applying to the results the principles that have been developed above. One interesting point, seemingly confirmative of this view, is the relatively close agreement of the results by all of the methods in the case of small animals, the rabbit, for instance, and the wider disagreement in the case of large animals, man, for instance; on account of the brevity of the mixing period, the smaller the animal the more apt is the reading to be made after mixture has become complete, and the more complete is the yield of hemoglobin to perfusion apt to be. The views developed above also seem to account for the exactness with which most of the methods, which give wholly different values for the total blood volume, measure a hemorrhage or a transfusion of known volume (12), (47), (79, etc.). Finally attention should be called to the wide discrepancy in many instances between the blood volume as derived by direct and by indirect methods. This, again, is especially obvious in the case of larger animals. In the dog, for example, the washout determinations rarely exceed 8 per cent of the body weight, whereas many of the indirect deter-

TABLE 1

SUBJECT	METHOD	CASES	WEIGHT		MIXING TIME	BLOOD WEIGHT / BODY WEIGHT		REMARKS
			Range	Average.		Range	Average	
			kgm.	*kgm.*	*min.*	*per cent*	*per cent*	
Man	Washout (86)	2				7.2– 8.2	7.7	
Man	NaCl-hemat. (28)	4	52.5 –64.0	58.8	4–5	7.7– 8.7	8.3	Inj. 5 min.
Man	NaCl-Color. (2)	5	54.4 –67.5	58.0	0–3	4.7– 5.8	5.2	Inj. 2–6 min.
Man	NaCl-Refr. (29)	19	49.0 –75.0	62.6	4	6.3– 8.4	7.4*	Inj. 4–5 min.
Man	Gluc.-NaCl (33)	3	41.3 –60.1	53.6	5–10	5.1– 5.9	5.5*	Inj. 10 min.
Man	CO. (55)	14	58.2 –89.0	72.2	2–3	3.3– 6.3	4.8	3.3 obese
Man	CO. (2)	4	65.0 –77.0	70.3	3–4	5.0– 6.0	5.6	
Men	CO. (87)	9	76.5 –57.0	65.9	?	3.9– 8.8	5.5*	
Women	CO. (87)	3	44.0 –75.0	60.3	?	2.6– 7.0	4.9*	
Women	CO. (88)	6	44.0 –70.0	57.0	?	4.6– 6.4	5.6*	
Man	CO. (63)	1	65.0	–	+	7.57	7.6*	Long mixing
		1	70.0	–	+	8.43	8.4*	
Man	CO. (62)	4	51.6 –79.5	66.3	20+	6.3– 8.3	7.3*	Ele. 1520 M.
		4	51.6 –75.9	63.9	20+	7.7– 8.8	8.3*	Ele. 3580 M.
Man	CO. (6)	6	72.7 –60.9	65.4	±10	5.5– 7.4	6.3*	
Man	CO. (59)	20	6–16 yrs.	–	+	6.1– 8.2	6.9	Boys 7.0; girls 6.7
Man	Antitox. (89)	9	38.5 –83.0	58.1	?	5.9–10.2	8.7	Ele. 180 M.
Man	Antitox. (72)	9	52.0 –88.7	67.2	15	8.9–10.7	9.8	Ele. 519 M.
Man	Antitox. (73)	10	– –	–	–	5.7– 9.1	7.9	
Men	Vital Red (79)	18	76.3 –47.4	60.4	3 & 6	8.2–10.4	8.8	
Monkey	NaCl-Sp. Gr. (27)	1	–	1.95	?		9.0	Young
		1		2.16	?		7.3	
Dog	Washout (8)	5	2.11– 5.95	3.31	–	6.6– 8.1	7.4	
Dog	Washout (24)					6.4– 7.0		

Dog	Washout (90)					7.1– 8.9		
Dog	Washout (91)	1	2.47	—			7.9	
Dog	Washout (91)	2	0.79– 1.46	—		8.7– 8.0	8.3	Pups
Dog	Washout (92)	2	1.85– 4.28	—		8.9– 8.4	8.6	
Dog	Washout (92)	1	3.1	—			7.9	Pregnant
Dog	Washout (92)	3	0.40– 0.45	—		5.6– 6.1		Pups
Dog	Washout (93)	2	11.5 –15.6	—		6.9– 6.9	6.9	1 sick
Dog	Washout (93)	1	4.9	—			8.2	Lactating
Dog	Washout (17)	5	2.35– 6.18	4.25		7.0– 9.9	8.3*	Young
Dog	Washout (18)	61	8.0 –39.5	20.3		4.7– 8.6	6.8	
Dog	Washout (2)	3	5.78–10.35	8.61		7.8– 8.7	8.2	
Dog	NaCl-Hb. (2)	3	5.78–10.35	8.61	?	7.9– 8.6	8.2	
Dog	NaCl-Sp. Gr. (27)	3	7.94– 9.96	8.89	?	6.8– 6.9	6.8	
		1	6.29		?		12.8	Young
Dog	Serum repl. (42)	2	5.90– 8.60	7.2	30?	7.1– 7.1	7.1*	
Dog	Gum-NaCl repl. (43)	6	5.00– 9.75	7.25	—	6.4– 7.9	7.3	
Dog	CO. (53)	9	10.1 –20.3	18.8	15	7.7– 9.7	8.6*	
Dog	CO. (2)	4	5.7 –11.5	9.7	?	7.4– 9.5	8.4	
Dog	Gum Grav. (41)	18	4.6 –20.0	8.6	10	8.3–11.4	9.7	
Dog	Gum-Gel. Refr. (75)	21	7.0 –20.5	12.7	3–5	7.7–12.0	10.3*	
Dog	Vital Red (47)	22	7.3 –22.0	15.1	4	8.9–12.1	10.6*	
Dog	Vital Red (43)	4	6.0 – 9.7?	?	4?	8.4– 9.4	8.9	Uncorrected
Dog	Congo Red (43)	6	4.7 –16.5		?	7.0– 8.2	7.6	Uncorrected
Cat	Washout (6)	1					6.9	
Cat	Washout (24)					4.6– 4.8		
Cat	Vital Red (43)	2	3.8		?	6.0– 6.6	6.3	Uncorrected
Cat	Congo Red (43)	3	1.7 – 3.0		?	5.5– 5.5	5.5	Uncorrected
Cat	Gum. Grav. (41)	8	1.5 – 4.3	3.04	10	4.5– 6.8	5.5	
Sheep	Antitox. (31)	2	7.0		40?	6.3– 6.7	6.5	
		1	37.0		40?	6.56	6.6	
Rabbit	Washout (94)	15	0.31– 1.74	1.08		2.2– 5.3	3.9	

TABLE 1—*Concluded*

SUBJECT	METHOD	CASES	WEIGHT		MIXING TIME	BLOOD WEIGHT / BODY WEIGHT		REMARKS
			Range	Average		Range	Average	
			kgm.	*kgm.*	*min.*	*per cent*	*per cent*	
Rabbit	Washout (8)	5	0.67– 1.07	0.80	—	4.8– 6.1	5.6	
Rabbit	Washout (90)					4.4– 5.9		
Rabbit	Washout (9)	9	0.47– 0.91	0.63	—	7.2– 8.7	7.8	Note weight
Rabbit	Washout (9)	11	1.88– 2.58	2.24		3.7– 4.9	4.3*	= 98 per cent
Rabbit	Washout (14)	20	1.82– 3.25	2.62		4.2– 5.7	4.9*	
Rabbit	Washout (13)	10	0.15– 0.48	0.33		5.2– 7.1	6.0*	
Rabbit	Washout (13)	7	0.57– 0.85	0.70		5.1– 5.6	5.4*	
Rabbit	Washout (13)	8	1.06– 1.97	1.56		3.6– 5.3	4.6*	= 93 per cent
Rabbit	Washout (13)	16	2.05– 2.43	2.25		3.8– 5.1	4.5*	
Rabbit	Washout (13)	6	2.50– 2.94	2.69		4.3– 5.7	5.0*	
Rabbit	Washout (13)	5	3.00– 3.50	3.23		4.4– 5.8	5.0*	
Rabbit	Washout (10)	5	1.51– 1.92	1.77		5.0– 6.3	5.4*	
Rabbit	Washout (10)	5	2.24– 2.92	2.59		4.7– 5.6	5.0*	= 99 per cent
Rabbit	Washout (10)	2	3.10– 3.15	3.12		4.8– 4.8	4.8*	
Rabbit	Washout (42)	2	1.98– 2.25	2.11		6.4– 5.7	6.0*	
Rabbit	NaCl-Sp. Gr. (27)	4	2.29– 3.57	3.06	½	6.6– 7.5	6.9	
		3	1.06– 2.04	1.66	½	7.6–16.5	11.3	Young
Rabbit	Serum repl. (42)	10	1.86– 2.80	2.33	30	5.0– 6.3	5.9*	
Rabbit	Hemorrhage (10)	9	1.23– 3.25			4.6– 6.2	5.1*	
		1	0.67			7.5	7.5	Note weight
Rabbit	CO. (48)	3			?	6.3– 7.0	6.7*	8.6* per cent by NaCl
Rabbit, male	CO. (12)	8	2.18–27.8	2.5	?	4.8– 6.4	5.4*	
Rabbit, female	CO. (12)	14	2.17– 3.76	3.11	?	4.3– 7.4	5.8*	
Rabbit, male	CO. (11)	7				4.4– 6.4	5.1*	

Rabbit, female	CO. (11)	4				4.0– 6.5	5.6*	
Rabbit, male	CO. (61)	7	1.50– 3.01	2.09	±10	5.0– 5.5	5.2*	
Rabbit, female	CO. (61)	5	1.25– 2.63	2.09	±10	4.3– 5.8	5.3*	
Rabbit	Antitox. (3)	2	2.20– 3.85		40?	5.3– 7.4	6.3	
Rabbit	Gum Grav. (4)	7	1.80– 3.00	2.31	10?	4.3– 6.6	5.4	
Rabbit	Gum-Gel. Refr. (75)	14	2.5 – 3.8	3.3	5–30	6.2– 8.1	7.1	
					5		6.5	
Rabbit	Vital Red (95)	23	1.52– 3.13	2.38	?	4.2– 5.8	5.1*	
Rabbit	For. Serum (74)	24			2–8	5.2– 6.8	6.0*	
Guinea pig	Extract. (24)						5.8	
Guinea pig	Extract. (90)					4.2– 4.2		
Guinea pig	Extract. (10)	9	0.21– 0.82 *gms.*	0.44 *gms.*		3.5– 5.5	4.3*	
Rats	Extract. (96)	129	37.2–267.5			5.6– 7.4*		
Mice	Extract. (10)	19	11.8 –29.3	23.1		4.9– 7.4	6.1	
Mice	Antitox. (3)	1	10.0				6.6	

* The relation of blood content to body weight by some investigators is expressed as the ratio of blood volume in cc. to body weight in grams; by others, as the ratio of blood weight in grams to body weight in grams. Not infrequently it is impossible to determine which method is employed. We feel that the relation should be that of blood mass to body mass, i. e., of weight of blood to weight of body, and wherever the other method clearly has been employed, we have taken the liberty of making the conversion by multiplying the figures by 1.056. The asterisk indicates the figures so derived.

minations lie in the vicinity of 10 per cent. To be sure, practically all of the sources of error inherent in the former method tend to produce low values; the differences, though, seem to be too large to be chargeable entirely against the washout method.

RELATIVE BLOOD VOLUME

The determination of the relative blood volume is based upon the assumption that during a sufficiently limited period of time the total number of red corpuscles in circulation is constant and that all relatively rapid physiological changes in the blood volume are effected by the passage of fluid back and forth between the blood and the tissues.

The validity of the assumption upon which this principle is based is by no means universally granted. Despite seemingly convincing evidence both old (for the literature see Hayem (1) and Friedemann (97)) and recent (98), (99), (100), that in the normal resting organism the red cells are evenly distributed through the entire circulation, there are those (the literature of this phase of the subject is fully reviewed by Lamson down to 1915 (101)) who maintain that there are stores of red cells subject to call. It will be possible to consider only those phases of this question that bear very directly upon blood volume problems, and which have recently been the subject of discussion. Lamson and collaborators (84), (101), (102), (103) finding that the increase in the red cell count that rapidly develops after the intravenous administration of adrenalin is accounted for only in part by a decrease in plasma volume as determined by the vital red method, and that the increase is effected through the medium of the liver, and only when it is accessible to the adrenalin, conclude that the "liver is the organ which supplies the body with red cells to meet its acute demands." They do not show by direct examination of the blood that the liver contains such a store; as a matter of fact it has been shown that after the injection of adrenalin the capillaries of the liver not alone are not depleted of red cells, they (104) and the mesenteric capillaries also (105) may actually be greatly engorged, and at a time the cell count in the general circulation is high. In other words "polycythemia" seemingly occurs not because of liberation of cells stored in the liver, but despite an abnormal accumulation of cells there and elsewhere. This accumulation of cells in the capillaries presumably is comparable to that which occurs whenever the blood stream is markedly slowed, as, for instance, by cold (106), by obstructing the aorta or the vena cava (107), in shock (100), etc., etc.; and presumably the "polycythemia" is due to the transuda-

tion of plasma that occurs under the same circumstances (27), (108). To be sure, Lamson finds that the decrease in plasma volume is not always sufficient to account for the concentration of red cells. But it seems precarious to decide so important a question upon the basis of results obtained by a method which seemingly indicates too small a relative cell volume at a time when, as a result of hemorrhage, the red cells are sparse (see 47, p. 218); for it is not impossible that, *per contra*, it may indicate too large a cell volume when, as a result of transudation, the red cells are densely packed. Other observations taken as evidence for the existence of stores of red cells such, for example, as the early increase in hemoglobin during muscular exercise (109), (110) (interesting in view of the opening up of unused capillaries which contain no red cells (111)), abdominal massage (110), and diminished oxygen pressure, can be accounted for, at least equally as well, upon the basis of alteration in the amount of blood plasma (62), (65), (99), (112), (113). Scott argues (112) that if masses of reserve corpuscles are hidden away we would expect them to be called out into the general circulation in times of stress, as for example, after hemorrhage; and that they would be washed out into the general circulation by copious injections of Ringer's solution; but neither he nor Mendel and collaborators (32), (114) get any evidences of such effects.

Not infrequently alterations in the relation of hemoglobin to the red cell count have been noted which seemed to be explicable only upon the basis of the entrance of new red cells into active circulation. Scott, Hermann and Snell, who give the literature (99), maintain that this usually is attributable to technical errors. The change in the relation of hemoglobin to cell count and the reduction in the size of the red cells following the injection of adrenalin, as observed by Lamson (101), likewise are not necessarily indicative of the presence of new cells, or of cell division. In so far as these changes are real, it is possible to account for them quite as well by assuming that the sedimentation and jamming (115) caused by slowing of the blood flow, constriction and plasma absorption, hold back first the heavier and larger corpuscles.

It is clear, however, that in so far as slowing of the blood stream causes red cells to accumulate in the capillaries and venules, the results obtained by means of the relative method will fail to indicate changes in blood volume. Indeed, when the condition becomes extreme, as in the stasis of shock, including that produced by massive doses of adrenalin, even the absolute methods fail (108). Under such conditions altering the blood supply to an organ containing like the liver, highly permeable

capillaries (116) might very well so alter the relation of stagnation of red cells to transudation of plasma there as to cause the very changes in the general circulation which have led Lamson and Nagayama (84) to discountenance blood volume determinations in general.[2]

Methods of estimating the blood volume have been based by Vierordt upon the circulation time and contraction volume (117), by Tarchanow upon concentration of the blood associated with the loss of water during a sweat bath (118), by Arthaud upon the relation of blood pressure to pulse rate (119), by Morawitz upon gravitational changes in arm volume (120), and by Cardenal upon the dilution of the blood following the ingestion of water (121). Most of these methods rest upon unjustifiable inferences or upon an incomplete analysis of the processes involved (122).

REGULATION OF THE BLOOD VOLUME

Although the volume of the blood responds quickly to physiological needs and pathologically may be subject to very great alterations, observation indicates that the healthy organism strives to keep the general level constant. Indeed, Chisholm (96) finds that the blood volume is less variable than the weight of the kidneys, liver and spleen considered as per cent of the total body weight. Richet and collaborators (18) alone maintain that the blood volume is subject to great variation. Views held with regard to the mechanisms concerned in maintaining this constancy of the blood volume have recently been reviewed by Friedemann (97) and by Bayliss (40) so that only very recent contributions to the subject need be considered here.

Bayliss emphasizes in his review the important rôle played by colloids through their osmotic pressure in maintaining the blood volume, as exemplified by the persistence with which isotonic gum acacia solu-

[2] Bock (140) finds by the vital red method in diseases presenting extremes of total red cell volume a plasma volume approximating the normal, and, consequently concludes that variations in the total blood volume are due for the most part to changes in the corpuscular content of the blood. His conclusion is so worded as to seem to include not alone the abnormal variations studied by Bock, but, and without justification, the normal variations also. Furthermore, this result does not cast doubt, as Bock seems to believe, upon the value of percentile changes in hemoglobin as an index to the relative blood volume; for the conditions he has studied are not those in which the relative blood volume method is held to yield unambiguous results (see introductory paragraph on this subject).

tions remain in the circulation. Additional evidence in favor of this point of view is furnished by experiments showing that the presence of hypertonic gum acacia in the circulation retards transudation of plasma both in normal and in shocked animals (108), and causes an expansion of the blood volume (77). This expansion, though, is remarkably slow and is less than the acacia theoretically could produce through osmotic action (77). The fluid that enters the blood stream brings with it crystalloids in the same concentration, presumably as they occur in the tissue fluids, and usually a very small amount of protein, in addition (30). These observations, together with the observation that a hypotonic solution of acacia also is fairly efficient in maintaining an expanded blood volume (123), seem to indicate that the vessel walls are not wholly impermeable to colloids and that alterations in colloidal equilibrium are not of themselves sufficient to bring about the rapid interchanges of fluid between blood and tissues that occur in association with physiological processes. Kruse (124) maintains that this action of acacia is due in part to interference with renal function. But acacia does not stop diuresis (30), (41), (76), (123); furthermore, it is well known that absence of the kidneys does not delay the elimination of injected solutions from the circulation (114). The expansion caused by the hypertonic acacia can be hastened by combining with it a hypertonic crystalloid (108). There are many instances, additional to those referred to by Bayliss, illustrating the usefulness and innocuousness of gum acacia as a means of maintaining the blood volume (21), (30), (32), (123), (125), (126), (127), (128), (129), (130), (131). Contrary to de Kruif (132) and to Bayliss (40) but in agreement with Kruse (133), Karsner and Hanzlik (134) find that, in common with, though to a lesser degree than, a long list of similar substances, gum acacia in 1 per cent solution causes hemoagglutination *in vitro* and elicits an anaphylactoid reaction. While the latter authors advise caution in the use of acacia, they give no specific instances of injurious consequences. Mann (135) and Richet and collaborators (136), (137) alone seem to feel that, in lieu of blood, serum is superior to gum acacia. An interesting addition to the data employed by Bayliss in developing this subject is the observation by Smith and Mendel (32) that whereas all injected salt solutions leave the circulation rapidly, the very ones that diffuse with difficulty through the gut (138) are also the slowest to leave the circulation.

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THE SUGAR OF THE BLOOD

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From the moment it enters the blood of the portal system until its oxidation is complete, carbohydrate is subject to constant changes. These lead to the production of a long chain of intermediate products of which only two are of sufficient stability that they accumulate in the tissues and fluids of the body in amounts capable of being measured by chemical means. These substances are glucose and glycogen, the former being mainly dissolved in the circulating fluids, and the latter mainly deposited as colloidal masses within the tissue cells. Although estimations of the amounts of these substances can furnish us only with fragmentary knowledge of the history of carbohydrate in the animal body as a whole, it is nevertheless the case that the information thus gained is of great value both in understanding the general nature of the normal process and in detecting the factors concerned in its breakdown.

Most of the recent work has been done by studying the concentration of sugar in the blood, and the present review will concern itself primarily with this aspect of the problem.

Addition of glucose to the blood may be the result of: *a*, absorption from the intestine; *b*, hydrolysis of glycogen particularly in the liver (glycogenolysis); *c*, new formation of glucose out of non-carbohydrate substances such as amino acids (gluconeogenesis). Disappearance of glucose may be the result of: *1*, oxidation in the tissues; *2*, excretion, mainly by the kidneys; *3*, polymerization into glycogen; *4*, conversion into non-carbohydrate substances such as fat. The blood sugar is determined in order to throw light on the behavior of one or other of these processes but the results can be of value in doing so provided only that the processes other than that under investigation are maintained in a constant level of activity. Failure to recognize this principle has been responsible for a considerable amount of confusion in the interpretation of the causes for variations in the concentration of the blood sugar.

In a broad sense, a discussion of the sugar of the blood would involve a consideration of all of the processes just enumerated, but obviously this is far beyond the scope of the present article. We must more or less arbitrarily confine our attention to a study of those aspects of the subject which in recent years have seemed to be of the greatest importance in affording us means for further progress.

These introductory remarks will serve to indicate the plan of the present article. After a brief review of the principles of the methods used for estimating the blood sugar and a comparison of their relative degrees of accuracy, we shall consider how the glucose is contained in the blood—that is, its distribution between corpuscles and plasma and whether it is in simple solution or is combined with other substances—and its stability after the blood is removed from the body (glycolysis). We shall then study its concentration in the normal animal before and after the taking of food and the relationship existing between the sugar of the blood and urine under these conditions. Finally, we shall consider in what way the concentration of blood sugar becomes altered in disease and how far these alterations may be of value in diagnosis and treatment.

Methods for measurement of concentration. Without going into detail it is important to consider briefly the general principles of the methods that are most used today for estimation of the blood sugar and to compare their accuracy. All the methods depend on the reducing properties of glucose and they may be divided into two groups according to the means employed to measure the reducing power. In one, which we may call the *titrimetric* group, the reduction of cupric to cuprous oxide in alkaline solution is determined by titrating the latter, either with ferric sulphate and permanganate as in Bertrand's method, or with free iodine as in Bang's (5) and Maclean's (36) methods and their various modifications. In the other, which may be termed the *colorimetric* group, either the development of a red color due to reduction, in the presence of sodium carbonate, of picric acid to sodium picramate (33), (45), (46), (48) or of a blue color due to the action of cuprous oxide on Folin's phenol reagent (tungstic acid) is measured quantitatively, by means of a colorimeter (13).

In the case of the titrimetric methods it is necessary first of all to remove the protein by precipitation, for which purpose colloidal iron has been found the most suitable reagent, and then to heat the protein-free filtrate with the alkaline cupric solution. In the case of the picric

acid methods, the same reagent that is used to precipitate the protein remains in excess in the filtrate, and serves as the reagent which becomes changed in color by the reduction process. Provided the precautions that are laid down for each method by its author are taken, all of them yield entirely satisfactory results when pure solutions of glucose are used (and also when glucose is added to blood), but they do not agree so well when used for estimation of the sugar originally present in different samples of the same blood. The most recent comparisons of the results of different methods have been published by Höst and Hatlehol (23) and by Wesselow (61). The former observers compared four methods using blood samples from normal and sick individuals either with or without the addition of known quantities of glucose. Typical observations are given in table 1. The results in column *1* are for blood of a normal person, those in *2* for that of a patient suffering from uremic coma, and those in *3* for one suffering from diabetes.

TABLE 1

	METHOD	PER CENT GLUCOSE		
		1	2	3
Titrimetric	Bang	0.097	0.118	0.145
	Hagedorn	0.091	0.124	0.159
Colorimetric	Benedict	0.118	0.151	0.198
	Folin	0.105	0.121	0.188

It will be seen that the colorimetric methods usually give higher values than the titrimetric. These differences were usually observed in all of the thirty-five similar comparisons that were made. The results of the two titrimetric methods usually agreed with one another more closely than did those of the two colorimetric methods, and in the latter case those by the Benedict method were almost invariably higher than those by the Folin method. By all four methods glucose added to the blood was recovered with very little error (average 3.3 per cent for 83 estimations), which was usually in the direction of finding more than the quantity added. This indicates that the discrepancies in the estimations on the original blood cannot be due to a loss of glucose but rather because the colorimetric methods measure other substances than glucose. What these substances may be is not known. Creatinine might be largely responsible in the case of uremic coma but this is doubtful for, as pointed out by Myers (46), although "each milli-

gram of creatinine present in the blood introduces an error of about the same magnitude in per cent" (i.e., a blood with 20 mgm. creatinine would raise the blood sugar from 0.100 to 0.120 per cent), the error can only seldom be of consequence since it is rare to find more than 5 mgm. creatinine per 100 cc. blood."

Wesselow compared the results of the Maclean and Benedict methods, using blood and plasma. In the blood it was found that the results by Benedict's method were 45 per cent higher than those by Maclean's, and in the plasma, 12 per cent. These discrepancies became still more marked when a centrifuged mass of corpuscles was employed. Either the colorimetric method includes other substances than glucose, or reduction in the titrimetric is interfered with in some way. Wesselow believes that creatinine is largely responsible for the discrepancies. It should be pointed out that Benedict has recommended that the error due to creatinine could be avoided by treatment with charcoal or by discharging the creatinine color by means of acetone.

The preceding discussion of the value of the various methods will enable us to place a proper estimate on the results obtained by their use. We may safely conclude that for the great majority of clinical purposes any of the methods is sufficiently reliable provided the same one is always used. Now that inexpensive colorimeters are readily available there can be no doubt that the simple colorimetric method best meets the routine requirements of the clinic and of general practice,[1] but for research work the method of Bertrand or Maclean should possibly be employed.

How the glucose is contained in the blood. It is usually assumed that the reducing power of a protein-free filtrate of blood is proportional to the concentration of glucose. This assumption is however not entirely warranted since the blood is known to contain traces of fructose, aldehydes, ketones, glycuronic acid, uric acid, creatinine and perhaps other reducing substances. To determine the extent to which these substances may contribute to the total reducing power of blood, it has been attempted to destroy the glucose by fermentation with yeast and then determine the reducing power of the fermented solution. This method is however uncertain since, on the one hand, the yeast may itself contain reducing substances, or produce them during its action, and on the other, it may so change the non-fermentable reducing

[1] For details of rapid clinical method see Myers. For Myers test tube colorimeter, see Sorensen (65).

substances as to rob them of their reducing qualities (cf. (37), (23)). When we add to these possible sources of error the fact that fermentation of yeast is as a rule more or less incomplete we see how unreliable this method may be. As a matter of fact, investigators do not agree as to whether fermented normal blood filtrate does actually possess reducing powers.

The problem has been attacked by Stepp (58) by the application of an entirely different principle. This worker removed the proteins and other colloids from blood by phosphotungstic acid. He then determined the amount of residual carbon and compared this with the amount that would be expected by calculation from the sugar determined in another sample of the same blood by Bertrand's method. In certain cases of diabetes the residual carbon actually found was lower than that calculated from the sugar, thus indicating that the blood contained reducing substances with a lower percentage of carbon than glucose. In other cases the opposite relationship was found.

Assuming that the reducing power of a protein-free filtrate of blood is at least proportional to the glucose contained in the original blood, two questions present themselves for consideration; first, is all of the sugar in simple solution or is a part of it in some sort of combination with other blood constituents; and secondly, how is the sugar distributed between the corpuscles and the plasma?

Concerning the manner of existence of the sugar in blood, there are conflicting views. Thus: *a*, that it is all in simple solution as glucose; *b*, that part is in simple solution as glucose, the remainder being in combination, either very loosely or more firmly, with protein; *c*, that part is in simple solution as glucose the remainder existing as disaccharide or polysaccharide (e.g., glycogen, dextrines). So far as our present knowledge goes the only way by which the problem can be directly investigated is by studying the diffusibility of the blood sugar through membranes. When normal or diabetic blood is placed in a dialyzer with a sufficient amount of isotonic saline solution outside, the sugar all disappears from the blood in 24 to 48 hours; or when the outside fluid is limited in amount, diffusion occurs until the percentages of sugar within and without the dialyzer are equal, as in the striking vividiffusion experiments of McGuigan and Ross (40) and of J. J. Abel (1). There are certain theoretical objections to accepting the results of these experiments, as bearing on the present question, but most of them are met in the experiments of Michaelis and Rona (41). These workers placed equal quantities of fresh unclotted blood in a series of

small dialyzers, each of which was then immersed in an isotonic saline solution containing glucose in percentages which varied between 0.05 and 0.2 in the different solutions. After dialysis for 24 hours at low temperature, analysis of the specimens of blood for sugar revealed the fact that the percentage had become changed in all save that one which had been dialyzed against a solution containing the same percentage of glucose as the blood itself. When the dialysis occurred against solutions containing a lower or a higher percentage of glucose than the blood, the percentage in the latter fell or rose (differential dialysis). This would seem to prove that all the sugar in blood must be in simple solution.

Objections have however been raised against these experiments by Kleiner and by Hamburger. Kleiner (28) points out that although the blood sugar is shown to come into equilibrium with glucose solutions after prolonged periods of dialysis, this does not necessarily mean that the rate with which the diffusion occurs at the various stages of the process is the same for the glucose naturally present in blood as for glucose artificially added to the blood. Assuming that the manner of combination of glucose, if such exists, would be similar in diabetic and normal blood, he compared *the rate of diffusion* of the sugar from diabetic blood with that of normal blood to which a sufficient amount of glucose had been added to make the percentage approximately equal to that of the diabetic blood. He did this by dialyzing 15 cc. quantities of "hirudin" blood against 1 liter of Ringer's solution at controlled temperatures, removing 2 cc. samples of blood at intervals of one hour for analysis. By plotting curves of the percentage of sugar remaining in the blood at the end of each period, it was found that the curve for normal blood *plus* glucose descended in a perfectly regular manner from hour to hour, more rapidly at first and slower later, but that the curve for diabetic blood was irregular because the dialysis was delayed or completely interrupted during one or more periods, usually that of the second hour. These differences between the normal and the diabetic bloods were exaggerated by delaying the dialysis either by use of thick parchment dialyzers or by adding a certain amount of glucose to the outside fluid. It is difficult to interpret these results. Kleiner thinks that they indicate that some at least of the sugar in the diabetic blood must be in a combined state and he infers that if such a compound is present in diabetic blood there is a possibility that it also exists in normal blood. The observations are interesting but scarcely conclusive.

Hamburger (18) raises objection to the dialysis experiments on the ground that although it diffuses through parchment or collodion, the sugar may really be combined with colloids, and he quotes Bechhold's observations showing that some colloidal substances can diffuse through membranes. In observations in which the kidney of the frog was perfused through the renal artery with isotonic solutions containing glucose, this investigator found, in the fluid flowing from the ureters, somewhat less glucose than was present in the perfusion fluid when ordinary Ringer's solution was used, and that the retention could be increased, so that the urine became free of glucose by raising the percentage of bicarbonate in the perfusion fluid to 0.285, which makes it of the same reaction as frogs' blood. Alteration of the relative amounts of calcium and potassium in the perfusion fluid was also found to affect the permeability.

The chief reason why so much interest has been taken in the possibility that some of the sugar exists in combination in the blood plasma, is that it might serve to explain the supposed absence of sugar in urine under normal conditions. But now that it is firmly established that normal urine *does* contain sugar and that the concentration of this runs at least approximately parallel with that in the blood, the reason for assuming that some of the blood sugar is combined no longer exists. Cushny's observations on the filtration of blood serum through collodion filters further support the view that sugar filters through the glomerular epithelium.

Quite apart from the possibility that some of the sugar may be loosely attached to other substances, several of the older authors, notably Pavy (47a) and Lepine (31), believed that a portion of it exists more firmly combined so that it can be detected only after treatment of the blood with strong (hydrolyzing) reagents or with specific enzymes. Pavy found that the concentration of sugar was decidedly increased by boiling the blood with mineral acid and Lepine states that decided increase also occurred when the blood was simply allowed to stand, especially at a moderate degree of warmth. I have never succeeded in confirming this latter observation. For example, I have compared the reducing power (by Bertrand's method), of blood collected in ice-cold water and immediately precipitated with colloidal iron, with that of blood simultaneously collected and then allowed to stand in the incubator for 15 to 40 minutes before precipitation (37a). In a series of nine observations, partly on normal and partly on diabetic blood, the percentage reducing power was invariably found to be

less after incubation than before, because of glycolysis. Lepine also states that a similar increase may occur in the free sugar of the blood during its passage from the inferior vena cava to the carotid artery. If a spontaneous increase in blood sugar does really occur, the probable cause is that the blood circulating in the body contains substances of the nature of dextrine or glycogen, upon which diastatic enzymes act so as to produce reducing sugars. These glycogen-like substances would be expected to be more plentiful in blood taken from the hepatic veins than elsewhere, since they could not exist for long because of the powerful diastatic enzymes present in blood. It is of interest in this connection that Huber and I (24) have been able to confirm the observation of Ishimori, working with Hofmeister, that material giving Best's carmine stain for glycogen can be observed to be extruded from the liver cells into the hepatic capillaries (sinusoids) when the glycogenolytic activities of the liver are excited, either by piqûre or by stimulation of the great splanchnic nerves. I may state however that I have not found it possible, by chemical means, to detect more than a trace of glycogen-like material in blood collected from the vena cava opposite the entrance of the hepatic veins under the above conditions. Large quantities of blood from markedly diabetic animals were collected immediately under alcohol, the precipitate digested with 30 per cent caustic potash, and the further isolation of glycogen carried out according to Pflüger's directions.

Distribution of sugar between plasma and corpuscles. Closely related to the question of the condition of sugar in the blood is that of its relative concentration in the plasma and corpuscles. Should equality of concentration of the sugar in plasma and corpuscles be found to exist, it would lend some support to the view that all of the sugar is in a state of simple solution. The evidence would not however be of the same weight as that of the dialysis experiments of Rona and Michaelis already referred to, since equilibrium between free and combined sugar might exist both within and without the corpuscle. For another reason however the comparisons are of interest, namely, that they will show whether the corpuscles may serve either as storehouses for sugar, as they do for oxygen, or at least as buffers in that they take up and give off sugar more slowly than the plasma. Although no sugar can pass between the blood and the tissue cells without first of all becoming dissolved in the plasma, it is possible that the diffusion occurs at such a rate that the corpuscles contain a perceptibly lower concentration

of sugar than the plasma, when the percentage in the blood as a whole is rising, and conversely a greater concentration, when the hyperglycemia is passing off. These considerations explain why the comparisons have been made both in normal blood and in blood containing excessive amounts of sugar.

There are two methods by which the partition of the sugar has been determined, the direct and the indirect. In the *direct method*, the blood is centrifuged and the corpuscular sediment washed free of adherent plasma by centrifuging with isotonic solution, the concentration of sugar being then separately determined in plasma and corpuscles. The method is highly fallacious partly because the corpuscles contain substances which vitiate the accuracy of the sugar estimations and partly because the corpuscles run the risk of losing much of their sugar either by diffusion into the solution that is used to wash them or by glycolysis (p. 218). In the *indirect method*, the blood is centrifuged and the percentages of sugar are separately determined in the whole blood and in the plasma; by also measuring the relative volumes of plasma and corpuscles the percentage of sugar in each of these is readily calculated.

The results obtained even by the indirect method can approximate the distribution of sugar in the living blood only when the separation into corpuscles and plasma is effected very rapidly after the blood has been removed from the body. Otherwise there must be a tendency to equalization of concentration within and without the corpuscles by diffusion.

Observations have been made on normal blood and on blood containing an excess of sugar. The results are not entirely consistent. A few of them for *normal blood* are given in the accompanying table.

It will be observed that the results vary somewhat according to the species of animal and the method employed for determination of the sugar. Usually the corpuscles contain either practically the same, or a lower concentration of sugar than the plasma, the difference being more marked in the blood of the dog than in that of man. Occasionally however, as in the second case in the table the corpuscles may contain more sugar than the plasma. It is said that there is no sugar in the corpuscles of the rabbit (29).

When glucose solutions are added to fresh human blood so as to bring the total concentration of sugar up to about that of a severe case of diabetes (0.3 to 0.5 per cent), Rona and Döblin (51) found that in 2 minutes much of the glucose had penetrated the corpuscles, although

not enough to equalize the partition between them and the plasma. Repeated washing of the corpuscular sediment, by centrifuging with isotonic saline, is said to cause the corpuscles to lose the power of absorbing glucose, indicating that some change has occurred which reduces their permeability or selective solubility.

The partition of sugar has been studied in the blood in various forms of *experimental diabetes* in laboratory animals (37) by numerous workers, and the results agree in showing that if any difference exists between corpuscles and plasma, it is in the direction of there being a greater concentration in the plasma. The discrepancy becomes greater as the

TABLE 2

ANIMAL	METHOD USED FOR MEASUREMENT OF REDUCING POWER	PERCENTAGE REDUCING POWER			AUTHORS
		Of whole blood	Of plasma	Of corpuscles by calculation	
Man	Colorimetric	0.12	0.118	0.121	Bailey (4)
Man	Colorimetric	0.12	0.105*		Bailey (4)
Man	Colorimetric	0.135	0.135	0.135	Gradwohl & Blavais (17)
		0.102	0.099	0.102	
		0.062	0.079	0.026	
Dog	Colorimetric	0.089	0.111	0.035	Wishart (64)
		0.096	0.100	0.087	
Man	Schenck's method, Knapp's solution	0.098	0.105	0.082	Tachau (59)
Dog	Bang	0.081	0.090	0.070	Tachau
Man	Colloidal iron and Bertrand	0.094	0.098	0.089	Rona and Döblin (51)

* The percentage of sugar in the whole blood remained consistently higher than that in the plasma during the hyperglycemia that was brought about by giving the patient who was suffering from hypothyroidism 240 grams glucose (cf. table 15 of Bailey's paper).

hyperglycemia becomes more marked but there does not seem to be any evidence to show that during the declining stages of hyperglycemia the corpuscles retain sugar longer than the plasma. Several of the researches in this field are however of little value either because the sugar was estimated separately in sediment and plasma or because uncertain methods for estimation of the sugar were employed. In post-prandial hyperglycemia in normal men Bailey (4) and Wishart (64) found in general similar results.

In cases of *diabetes mellitus* in man, the most reliable of the older work is that of Frank (14) who found decidedly more sugar in the

plasma than the corpuscles, and of Michaelis and Rona (41) who found only a trivial but variable difference between the two values. More recently, Tachau (59) found the following values in the blood of fasting diabetics:

	PLASMA	CORPUSCLES
1	0.138	0.120
2	0.173	0.125
3	0.165	0.165
4	0.185	0.181
5	0.323	0.230 (average)

In similar cases after the ingestion of carbohydrate-rich food, he found:

	PLASMA	CORPUSCLES
6	0.231	0.212
7	0.361	0.325
8	0.126	0.126
9	0.325	0.300
10	0.428	0.480
11	0.234	0.243

While the results in general confirm those already mentioned, they also show that occasionally the corpuscles may contain more sugar than the plasma. The factor upon which the distribution depends is probably the relative solubility of the sugar in plasma and corpuscular material respectively, rather than any specific permeability of the corpuscular envelope toward sugar molecules.

Glycolysis in blood. As has been pointed out elsewhere, the percentage of sugar in blood decreases after this has been drawn from the body, independently of the growth of microörganisms. The rate of decrease is more or less proportional to the temperature at which the blood is allowed to stand. In dog-blood about one-half the sugar disappears in $2\frac{1}{2}$ hours at body temperature. This *in vitro* process is called glycolysis and it has been thought by some (e.g., Lepine (31)) to be the continuation of an *intra vitam* process. It occurs readily in defibrinated blood or in blood prevented from clotting by hirudin, but it is interfered with by oxalate in concentrations over 0.1 per cent and is not exhibited by plasma or serum. Glycolysis is especially active

in the corpuscles, thus, all the sugar was found to disappear from the deposit of centrifuged (dog) blood at body temperature in ½ hour (37a). Both hemocytes and leucocytes probably participate in it. Suspensions of leucocytes (such as diluted pus) possess strong glycolytic powers (32) but hemocytes are also said to be able to show it in the absence of leucocytes (50). Laking the blood with saponin does not stop glycolysis but it ceases when the blood is laked with water although not if diluted with artificial plasma containing buffer substances (Locke's solution). Abundance of oxygen favors glycolysis although it can still proceed under anaerobic conditions. When the corpuscles are frequently washed, by centrifuging with isotonic saline, and then suspended in artificial plasma (Locke's solution) containing glucose, no glycolysis occurs. This brings to mind the observation that a similar treatment of the corpuscles also renders them incapable of absorbing glucose (p. 217), and would therefore suggest that glycolysis is an intracorpuscular process. The degree to which it occurs in any particular blood will therefore depend on two factors, first, the rate of absorption of glucose into the corpuscle and secondly, the glycolytic power of the corpuscular contents.

When all of these facts are considered it is not surprising to find that the rate of glycolysis varies considerably in the blood of different species of animals. Glycolysis is almost absent in the blood of the ox, the sheep and the pig (39). It varies also in the blood of different individuals of the same species, or even of the same individuals at different times, and it has been attempted to show in the case of man that this variability bears some relationship to the ability of the organism as a whole to metabolize carbohydrates. Its determination has therefore been thought to be of some value in the diagnosis of diabetes (31), but few agree with this view. The strongest evidence against it is the fact that even under the most favorable circumstances the reduction in percentage of glucose which occurs by glycolysis outside the body is very small compared with the reduction in the circulating blood after removal of the liver. Thus, Pearce and I (37c) found that 0.83 to 4.46 mgm. glucose disappeared from 100 grams blood per minute in animals from whom the liver had been removed whereas only 0.03 to 0.06 mgm. disappears from blood *in vitro* at the very beginning of the glycolytic process when it is most rapid. The presence of excess of glucose in the blood does not cause alteration in the rate of glycolysis.

The percentage of sugar in the (venous) blood of man and in that of the lower animals. Since carbohydrate-rich food markedly affects the blood-sugar level it is necessary for its comparison among different individuals to consider only those results obtained in blood removed some time after feeding. To ensure that the interval is long enough it is usually the practice in observations on man to use the blood in the morning before breakfast. In the following table are given some of the values recently obtained in healthy adults and children.

It will be observed that the maximum percentage reported by different observers is very much the same and with one exception is not above 0.12, the minimum on the other hand varies, and may go as low as 0.044.

TABLE 3

NUMBER OF CASES OBSERVED	VARIATIONS IN BLOOD-SUGAR	METHOD USED	OBSERVERS
30 adults	0.05 –0.12	Original Lewis-Benedict	Gettler and Baker (16)
	0.06 –0.11	Bang micro	Hopkins (22)
100 adults	0.044–0.12	Modified Lewis-Benedict	Cummings and Piness (10)
500 adults	0.09 –0.11	Modified Lewis-Benedict	Myers and Bailey (45)
16 adults	0.09 –0.12	Modified Lewis-Benedict	Denis, Aub and Minot (11)
	0.085–0.11		
113 adults	0.07 –0.14*	Original Lewis-Benedict	Williams and Humphreys (63)
	0.09– 0.11		Lewis and Benedict (33)
26 children	0.072–0.113	Original Lewis-Benedict	Bass (6)
100 children	0.087–0.118	Bang micro	Goetz (cf. 6)

* Some cases were examined one hour after taking food.

It is of interest to compare these values for human blood with those obtained by similar methods in the blood of lower animals, table 4.

By study of these figures the striking fact comes to light that the concentration of soluble carbohydrates in the circulating fluids is similar to that in man in representative animals from throughout the animal kingdom, as far down the scale as the Arthropods at least. The only exceptions are in the cases of the dog-fish (Squalus) and rat-fish (Chimaera). Some observers, Diamare for example, have stated that there is no sugar in the blood of the former and it is the case that in many specimens of this fish examined by us no reducing substance could be detected by the ordinary tests. In others, however, quite considerable quantities were found and in certain cases where none

TABLE 4

ANIMAL	PER CENT REDUCING POWER			METHOD AND OBSERVER
	Maximum	Minimum	Average	
Dog	0.102	0.073	0.085	Colloidal iron Bertrand, Oppler and Rona (47)
Dog (immediately after etherization)	0.146	0.075	0.111	Colloidal iron Bertrand, Macleod and Pearce (37[d])
	0.206	0.093		Keeton and Ross (26[a])
Cat	0.096	0.056	0.069	Phosphotungstic acid, E. L. Scott (56)
Cat (under cocaine)	0.0736	0.0546	0.0664	Scott's method, Schear (57)
Rabbit	0.13	0.08	0.10	Colloidal iron—polarization, Oppler (47)
	0.13	0.08	0.10	Bang (3)
Marmot:				
1. Hibernating			0.009	Dubois (cf. 5)
2. Active			0.117	
Birds (chicken)			0.23	Bierry and Fandard (5)
Tortoise	0.21†	0.05	0.102	Unpublished. Picric acid
Frog	0.05	0.02		Bang (3)
Fish:				
Teleostomi (carp)	0.145	0.058	0.090	Picric acid, Lang and Macleod (30)
(Lake trout)			0.081	Picric acid, Lang and Macleod (30)
Chimaera (rat fish)*	0.037	0.022	0.028	Picric acid, Lang and Macleod (30)
Elasmobranchus (dog fish)	0.038	0.000	Trace	Picric acid, Lang and Macleod (30)
Molluscs (horse clam)			Trace?	Picric acid, Bertrand, Lang and Macleod (30)
Arthropods:				
Cancer productus	0.081	0.039	0.040	Picric acid, Lang and Macleod (30)
Cancer irrotatus	0.11	0.06	0.074	Picric acid, Lang and Macleod (30)
Homarus Americanus			Trace	Picric acid, Bertrand, Lang and Macleod (30)
Octopus			0.032	Bierry and Giaja (5)

* Fish dead some time before blood removed.
† Turtle possibly asphyxiated.

could be detected by the usual chemical procedures (e.g., reduction of picric acid, Bertrand method), this became possible by using larger quantities of blood, extracting the evaporated protein-free filtrate with absolute alcohol, and measuring the reducing power of a watery solution of the evaporated alcoholic extract. In the closely related rat-fish (chimaera) a relatively low percentage of sugar was also found by the picric acid method. In contrast to these fishes, the higher forms, represented by the Teleostomi, gave results that are practically the same as for man. One might imagine that the concentration of blood sugar would gradually become less and less the lower one descended in the invertebrate scale, but this is apparently not the case since a percentage of about 0.07 was found (in the circulating fluid) of one species of crab (cancer irroratus) and from 0.04 to 0.08 per cent in another (cancer productus). When no sugar can be detected in the circulating fluids the possibility has to be considered that this is due to a process of rapid glycolysis setting in immediately the fluid is withdrawn for analysis, rather than to an actual deficiency in sugar. We gained the impression that glycolysis is very rapid in the circulating fluids of marine animals.

It should be pointed out that the identity of the so-called blood sugar of the lower forms has not been precisely determined although there is some evidence that it is closely related to glucose since it forms with phenyl hydrazine crystals of osazone that are indistinguishable in microscopical appearance from glucosazone. The interesting possibility must not be lost sight of, however, that the circulating carbohydrate, or a part of it, may be pentose rather than hexose, at least in those forms of invertebrates that live exclusively on vegetable foods containing pentosans in place of starches. Certain mollusks live on such food, and although in these animals we have not found it possible to collect a sufficient amount of circulating fluid in which to determine whether glucose is present, it is significant that the polysaccharide (glycogen) in the liver is apparently identical with that of the higher animals. This is also the case for still more primitive forms of animal (and plant life) (27).

That there is close correspondence in the concentration of soluble carbohydrates in the circulating fluids of such diverse groups of animals, emphasizes the importance of this substance in the animal economy. The well-known facts that sugar still remains in considerable percentage in the blood up to the last days of starvation in laboratory animals and that it is produced in excess out of amino acids in diabetes afford further evidence of its importance.

The blood-sugar curve following ingestion of carbohydrate. In the preceding pages attention is paid to the manner in which the sugar is contained in the blood and to its concentration under normal conditions. In the hope that the results might prove to be of clinical value, much attention has been paid in recent years to the quantitative behavior of the blood sugar during increased intestinal absorption. We shall now briefly review the main aspects of this work and consider the value of the results in relationship to the diagnosis of diabetic conditions. The first observations were those of Bang and his pupils (3) who found in rabbits that the sugar in the blood of the ear vein became perceptibly increased in about 15 minutes after giving starving animals 2 to 10 grams of glucose or of starch by stomach tube. The percentage of blood sugar continued to increase for about one hour, when it might attain to double its normal percentage (alimentary or post-prandial hyperglycemia), after which it gradually declined so as to regain the starvation level in about 3 hours. When starch or starch-containing foods were given to rabbits in which digestion was already in progress no effect on the blood sugar was observed to occur. These results clearly showed that the liver does not succeed in retaining as glycogen all of the glucose that is absorbed from the intestine into the blood of the portal circulation when the absorption is rapid, although it may succeed in doing so when the absorption is slow. The publication of these fundamental observations naturally stimulated many workers in the clinical field to investigate the behavior of the concentration of blood sugar in man before and following the ingestion of carbohydrates and other food stuffs in the hope that the results might be of value in diabetes and in other diseases. These investigations were happily rendered feasible by the introduction about this time of simple and accurate methods for the measurement of sugar concentration in small amounts of blood. Without any great inconvenience to the patient, samples of blood can be removed at frequent intervals from the arm veins, and the results of the analyses for sugar then plotted on coördinate paper as ordinates with the time intervals along the abscissa. Some of the results are given in the accompanying charts which have been redrawn from Bailey's paper (4). There are three aspects of the curves to be considered—first, the maximum height attained; second, the time at which this maximum occurs and its duration (after giving the carbohydrate); and third, the time required for the curve to return to normal. It will also be convenient to consider here the concentration of blood sugar at which glycosuria becomes established, the so-called renal threshold for sugar.

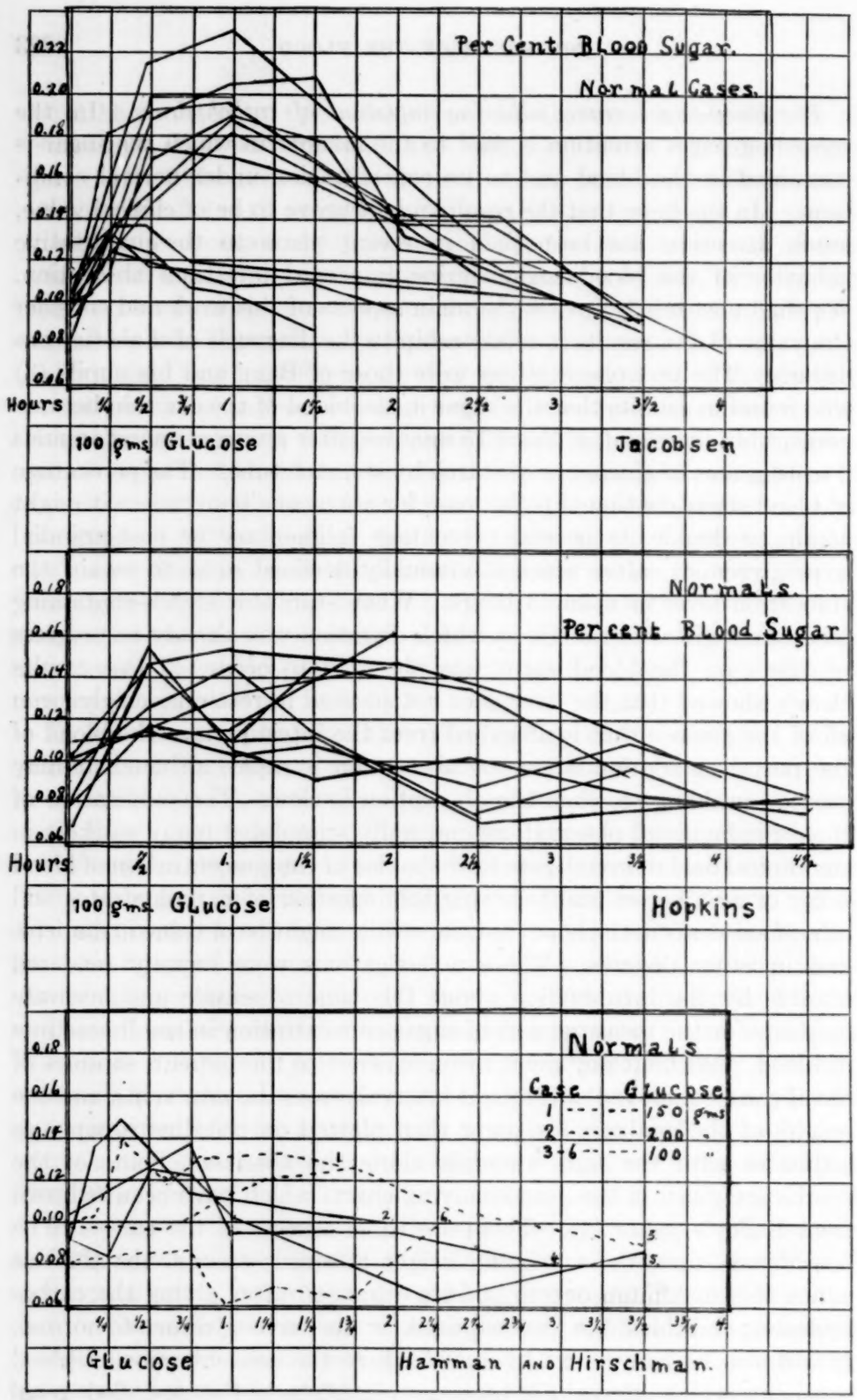

Fig. 1. Blood sugar curves for normal individuals following the ingestion of 100 grams or more of glucose. (From Bailey.)

The maximum height of the curve following the ingestion of 100 grams glucose varies greatly in different individuals. Thus, in four cases observed by Jacobson (25) it reached only to between 0.12 and 0.13 per cent, whereas in eight other cases it reached to between 0.17 and 0.23 per cent. In eight persons examined by Hopkins (22) the maximum stood between 0.11 and 0.156 per cent and in six, examined by Hamman and Hirschman (20), between 0.1 to 0.14 per cent. (Fig. 1.)

As would be expected, considerable irregularity was also observed in *the time at which the maximum occurred* and in *the duration of the hyperglycemia*. In Jacobson's observations the maximum occurred in about one-half hour and was of short duration, in those cases in which the maximum only reached a low level, but it might be delayed for one and one-half hours in the cases in which the maximum was high. The maximum was reached in about one-half hour in four of Hopkins' cases, but in four others it was decidedly later and the duration varied greatly. Cummings and Piness (10) examined the blood sugar in 58 normal subjects before, 1 hour and 2 hours after giving 100 grams glucose and they emphasize the fact that the rise in blood sugar attains its maximum (at about 50 per cent above the normal) during the first hour and drops to about one-half this during the second hour. Their method of blood analysis is however scarcely so reliable as that ordinarily employed. In Hamman and Hirschman's observations the maximum was reached in from 20 minutes to $1\frac{1}{2}$ hours and the duration of the hyperglycemia varied between 45 minutes and $3\frac{1}{2}$ hours, being more or less proportional to the height of the maximum and the time of its occurrence. If it were permissible to calculate an average from results that vary so greatly this would show that the administration of 100 grams glucose on an empty stomach should raise the blood sugar of a normal person to about 0.15 to 0.16 per cent in from 30 to 60 minutes and the normal should be regained in about 2 hours. The causes for the discrepancies are no doubt dependent mainly on inequalities in the digestive function such as the rate of discharge of the glucose through the pyloric sphincter, the volume of the intestinal contents, and the extent and nature of bacterial digestion. It is further evident from these results that if determinations of alimentary hyperglycemia are to be of any value for clinical purposes, the samples of blood must be removed for analysis at least at half-hour intervals. During the first hour after taking the sugar Bailey advocates blood examinations every quarter of an hour.

Bang also found that a second administration of glucose during the decline of the hyperglycemia produced by the first one, was followed

by a much less marked reaction. This has been confirmed by Hamman and Hirschman on normal and diabetic men. The significance of the result is that it indicates that assimilation of sugar causes stimulation of the sugar-destroying functions of the body. It is possibly partly for this reason that hyperglycemia is much less pronounced when sugar absorption is slow, as when starch is ingested. The first absorbed sugar stimulates the metabolic functions so that that subsequently absorbed is better assimilated.

The renal threshold. Before we proceed to compare the foregoing normal results with those obtained in diseased individuals, it will be advantageous to consider *the relationship which exists between the degree of hyperglycemia and the development of glycosuria.* It will be remembered that Claude Bernard was responsible for the view that no glucose appears in the urine until the concentration of the blood sugar reaches a certain level which has come to be known as the renal threshold for sugar. Justified by the inability of the great majority of investigators to demonstrate by the usual qualitative tests the presence of glucose in normal urine, this doctrine, until comparatively recently, has been almost universally subscribed to. The difficulties in the way of deciding whether normal urine contains glucose are dependent on the presence in this fluid of other substances capable of reducing alkaline copper solutions (i.e., creatinine, polyphenols, urochrome, glycuronic acid) as well as of substances which interfere with the proper precipitation of cuprous oxide. These interfering substances can be very largely removed by precipitation with mercuric nitrate (55), (7) or with phosphotungstic acid and lead acetate (47) or with picric acid (46) or with blood charcoal in the presence of 25 per cent glacial acetic acid or 15 per cent pure acetone (52), (37b). After such precipitation, the urine exhibits decided reducing properties but notwithstanding the large amount of attention that has been devoted to the subject it is not definitely known what proportion of this is due to glucose. By fermentation with yeast there is a certain diminution in the reducing power, which would indicate the presence of glucose, but the precise nature of the non-fermentable material is uncertain, although there is evidence (7) to show that it is carbohydrate in nature.

Although we cannot accurately measure the glucose excretion, it is very important to know whether the total of carbohydrates in the urine of normal animals bears any quantitative relationship to the percentage of sugar in the blood. Using the charcoal method for removal of the interfering substances, Macleod, Christie and Don-

aldson (37b) found that from 1 to 1.85 gram of such material were excreted in the 24-hour urine of two normal men living on mixed diets containing a considerable proportion of carbohydrate. Using the mercuric nitrate method, Benedict, Osterberg and Neuwirth (7a) found, in two normal men of 55 and 22 years of age, the total daily excretion to vary between 0.7 and 1.16 grams while living on ordinary diets, and to rise to a maximim of 1.6 grams when excess of carbohydrate was given. The ratio between the amount of fermentable and unfermentable sugar excreted also varied in relationship to the nature of the diet. The most significant results were secured by making the observations on urine voided every 2 hours during the day, the results being of the same nature in both of the subjects investigated, though quantitatively greater in the older man. After each of the three meals of the day, when these were rich in carbohydrates, an increase occurred in the fermentable sugar accompanied, at least in the forenoon, by a decided decrease in both the absolute and the relative amounts of the non-fermentable sugar. In the early morning (starving) urine the total reducing substance was small but the non-fermentable moiety relatively large. No definite relationship could be detected between the volume of the urine and the extent of the excretion of either fermentable or non-fermentable sugar. The increase in fermentable sugar might be so marked as to bring its concentration up to the level at which the ordinary clinical tests for sugar were pronounced. The important practical conclusion is drawn from the results that "the normal organism is truly diabetic in that it has no absolute tolerance for carbohydrate." In other words, the difference between the normal and the diabetic is wholly a quantitative one.

Observations were also made on the effects which followed ingestion of weighed quantities of glucose and of cane sugar, either on an empty stomach or along with food. In the case of the older man, on an empty stomach, although 20 grams glucose scarcely altered the total sugar excretion it invariably caused the non-fermentable moiety to become both absolutely and relatively diminished. This indicates that a change occurs in the nature of sugar metabolism in the body by ingestion of moderate quantities of glucose. With 40 grams glucose, the total sugar excretion increased but again the amount (both absolute and relative) of non-fermentable sugar fell decidedly. These effects were much less marked when cane sugar was given. There was some evidence to show that the ingestion of glucose increased the assimilative powers of the organism since ingestion of a second quantity did

not have so marked an influence upon sugar excretion as the first one. When 20 grams glucose were added to an average meal, the elimination of fermentable sugar was decidedly greater than when glucose was given on an empty stomach but here again the non-fermentable sugar decreased. This effect was brought out still more strikingly by adding 25 grams of glucose to each of the three meals: the fermentable sugar was greatly increased but the non-fermentable, diminished. In the case of the younger man these results were not so striking. The tolerance for glucose was much greater, for it required, on an empty stomach, 60 grams glucose to cause any noticeable effect on the urine, this being however of the same nature as in the older man. Taken along with food, on the other hand, 20 grams glucose were sufficient to have an effect. When 25 grams glucose were added to each meal of the day, there was no change in the total sugar excretion but a decline occurred in the non-fermentable moiety. Somewhat similar results were obtained in the case of two dogs, but we have not space to discuss them here.

The observations referred to show conclusively that the doctrine of a definite renal threshold must be abandoned. We must recognize that the normal urine contains sugar which becomes altered in amount under conditions which are known to cause a change in the blood sugar. The term glycosuria means nothing more than the presence of a sufficient percentage of sugar in the urine to give the ordinary qualitative tests and the term *glycuresis* as suggested by Benedict should be substituted to indicate the condition in which the sugar present in urine becomes increased above a certain amount. It is probable that in place of the usual qualitative tests for glycosuria the procedure which will in the future be employed in the diagnosis of incipient stages of diabetes will be to measure the total and the fermentable sugar excretion in the 24-hour urine. Provisionally we may say that if the total urinary sugar exceeds 1.5 grams in the 24-hour urine on an ordinary diet the case should be further investigated by testing, in 2-hour specimens, the effect which is produced by adding a certain amount of glucose to each of the meals of the day. But whether the procedure will prove itself to be more dependable than measurement of the blood-sugar curve following sugar ingestion has not as yet been established. What is needed now are observations on apparently normal individuals of various ages doing varying amounts of muscular work and living on various diets, to determine the precise relationship between alimentary hyperglycemia and glycuresis. Such observations will furnish us with

normal standards with which results obtained in suspected cases of diabetes can be compared and it is altogether likely that in this way we shall be enabled to detect a tendency to breakdown of carbohydrate tolerance at an earlier stage than is possible at present when such can be done only provided the glycuresis is so pronounced that the more or less arbitrary clinical tests for sugar in the urine react positive. As experience accumulates it will no doubt be possible to curtail considerably the number of urinary analyses that will be necessary to detect excessive glycuresis.

From what has been said, it will be clear that the sugar level at which a sufficient degree of glycuresis becomes established to cause the urine to react by the ordinary clinical tests for sugar (the renal threshold for sugar) is a more or less arbitrary value. Nevertheless it is of importance to determine it because it enables us to detect an alteration in the sugar-excretory function of the kidney. Such an alteration in the direction of a lowering of the threshold is known as *renal diabetes*. It is probable that many cases of slight glycosuria are really of the renal type and that the prognosis in such cases is vastly more favorable than when hyperglycemia is the cause of the glycosuria.

Attempts to determine the threshold have been made by Jacobson, Bailey, Hamman and Hirschman, etc. Sugar was found in the urine when the percentage in the blood reached 0.17 but not 0.16 by Jacobson. Hamman and Hirschman usually found the threshold at between 0.17 and 0.18 per cent blood sugar but occasionally it might be as low as 0.14 per cent. This variability in the normal threshold is emphasized elsewhere by one of these authorities. Williams and Humphreys accept 0.17 to 0.18 per cent as the normal threshold value. It is safe to conclude that the threshold in the majority of normal persons is at such a level that demonstrable glycosuria occurs when the percentage of sugar in the blood rises to 0.17. Bailey by using Myers' method for measurement of the reducing power of the clinically sugar-free urine, was enabled to study the problem in light of Benedict's results and he found that the percentages of sugar in the blood and urine run parallel until the former has risen to between 0.16 and 0.17, above which an excess of sugar appears in the urine and as the hyperglycemia passes off the decrease in the blood sugar precedes that in the blood. This relationship is shown in the accompanying curve of a typical case. According to these results the renal threshold represents a critical point in blood sugar below which the sugars of blood and urine run parallel but above which a large excess of sugar escapes into the urine. (Fig. 2.)

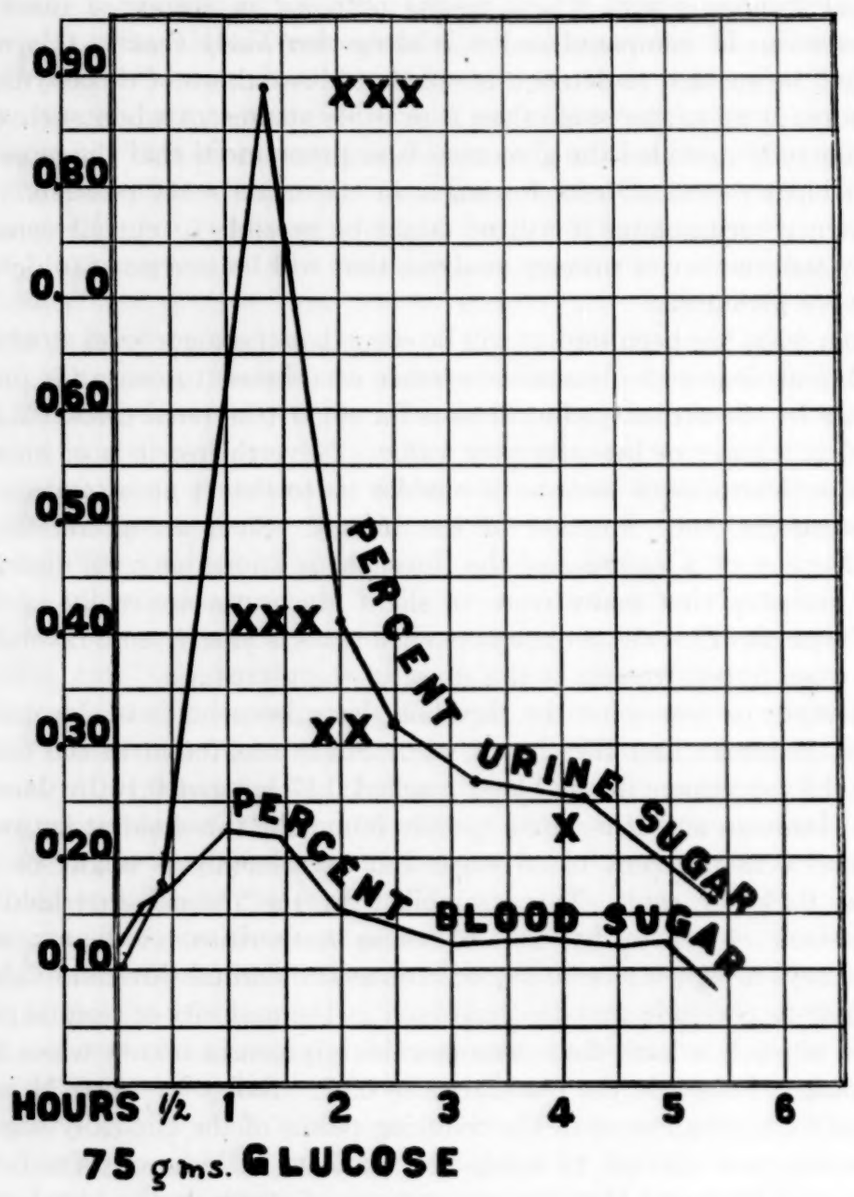

Fig. 2. Chart to show relationship between per cent sugar in the blood and in the urine. It will be observed that the threshold stands at about 0.17. Up to this point the sugar in urine and in blood runs parallel but above it excessive glycuresis occurs. Note also that the glycuresis is still marked after the percentage of sugar in the blood has returned well below the threshold level. The crosses indicate the degree to which the urine reacted positive for qualitative tests for sugar. (Redrawn from Bailey.)

While recognizing that determination of the blood-sugar curve is of undoubted value in the detection of disturbed conditions of carbohydrate metabolism, we must bear in mind that there are still many perplexing factors to be considered before we can adequately explain the rates of utilization and excretion of sugar in the body. Epstein (12) and Woodyatt (62), (53) have more particularly emphasized the necessity of considering, besides the concentration of sugar, *the blood volume*, that is, the increase or decrease in water. This will entail a change in the percentage relations of the various substances dissolved in blood, including the sugar, which may not run parallel with changes in total amounts. As a result of numerous observations on normal and diabetic men, Epstein came to the conclusion that it is the total amount of sugar in the blood, rather than its percentage, that is the factor which determines the escape of sugar by the urine. To determine the total sugar accurately it would be necessary to measure the blood volume at the same time that the sugar percentage is determined. This was not practicable when Epstein's work was done, but an attempt was made to arrive at it approximately by determining the relative blood volume (by the hematocrit) and then correcting the percentile values for blood sugar by the degree of change in blood volume. This corrected percentage will allow for changes in water content of the blood. In considering the quantitative relations between the sugar of the blood and urine in diabetes, Epstein regards the hyperglycemia as the sum of the greatest amount of sugar that can be present in the blood without giving rise to glycosuria (namely 0.1 per cent) plus an excess; and he says that a definite mathematical relation exists between the percentage of sugar in the urine and the (corrected) excess percentage in the blood.

Apart from the fact that these views do not adequately take cognizance of the presence of sugar in normal urine, as well as that the renal threshold of 0.1 per cent blood sugar chosen by Epstein is arbitrary, it is at present very difficult to see how variations in the total amount of sugar in the blood could influence either the rate of excretion or of utilization of the circulating sugar. Unless the percentage should change, how is the kidney to be stimulated or depressed in its sugar-excreting function? Epstein's observations cannot however be lightly dismissed, especially in light of the work of Woodyatt and his pupils. These workers found both in laboratory animals and in man that glucose could be injected continuously into the venous blood by means of a special injection apparatus at the rate of about 0.85 gram per kilo

per hour without causing glycosuria, and that beyond this tolerance limit and up to 2.0 grams per kilo an hour, a certain fraction of the injected sugar appeared in the urine varying with different individuals and, in the same individual, with different rates of injection. In the present connection the most significant point is, that variations in the quantity of water injected, while the injection of glucose in a unit of time was maintained constant, did not affect the rate of utilization or excretion of glucose. The administration of water was varied either by using a second injection apparatus or by injecting glucose solutions which differed in concentration between 10 and 40 per cent. As to how the tissues and kidneys are enabled to respond to changes in rate of supply of glucose rather than to change in concentration, it is difficult to say. As Woodyatt points out "Variations of the total quantity of a glucose solution of fixed concentration on one side of an ordinary dialyzer would not vary the rate at which glucose molecules diffused through it nor could the concentration be changed without affecting the rate of diffusion." It is suggested that the surfaces of contact between plasma and cells may increase or diminish in proportion as the plasma volume increases or diminishes, in which case the total number of glucose molecules impinging on the total cell surface will remain the same. Such considerations open up a new field of thought in connection with the whole question of exchange between cells and blood plasma, but it would be out of place here to speculate as to the possible mechanisms that may be involved. The marked changes in the lumen of the capillaries that Krogh has shown to occur, changes in the volume of the glomerular tuft and changes in volume and in the distribution of leucocytes are all to be considered in this connection.

The blood-sugar curve and the renal threshold in disease. In concluding the review it may prove of value to clinical workers if we briefly recapitulate some of the alterations which the post-prandial blood-sugar curve and the renal threshold for sugar have been found to undergo in diabetes and other diseases. In order that moderate deviations from the normal may be detected it is important that the specimens of blood for analysis be removed at least every half-hour until three have been taken and thereafter at hourly intervals. If collected only at hourly intervals from the start, as pointed out by Bailey, results that are normal may be obtained both in cases of renal diabetes and of early diabetes.

Diabetes mellitus. In three patients with mild diabetes after 100 grams glucose, Hamman and Hirschman (20) found that the curve rose more slowly than normal ($\frac{3}{4}$ hour to $1\frac{3}{4}$ hours) reached a decidedly higher level (over 0.2 per cent) at which it was apt to be maintained (forming a plateau) and then only slowly declined, the total curve occupying from 3 to 4 hours. In severe cases (receiving much less dextrose) the curve was of similar type the characteristic feature being its duration rather than its actual height. Glycosuria was an invariable accompaniment of the hyperglycemia. The renal threshold was usually normal in mild cases but once excessive glycuresis became established, as by ingestion of sugar, the kidneys continued to excrete excess of sugar after the blood sugar had fallen to considerably below the threshold (shown in Fig. 2, p. 230). These authors also point out that many severe cases of diabetes have a lowered threshold unless nephritis is also present, when it may be greatly raised and that superimposed doses of glucose are not necessarily followed by a steplike rise in blood sugar. This indicates that the first absorbed sugar stimulates the sugar destroying powers of the diabetic just as we have seen it to do in the cases of the normal person. This effect is however not so marked as in normal persons and it may be absent in severe cases of the disease.

Bailey (4) states that alimentary hyperglycemia is characterized by a rapid rise and fall in uncomplicated diabetes but that it becomes prolonged when there is renal involvement. At the same time the threshold for sugar is abnormally low in early diabetes so that glycuresis is excessive. This author concludes that tests of post-prandial hyperglycemia are of little clinical value in comparison with tests for glycuresis. In order to make these tests the sugar present in the urine should be determined by one of the methods described on page 226 at frequent intervals during 6 hours following the administration of 100 grams glucose. If this is coupled with a determination of the percentage of sugar in a specimen of blood removed the first thing in the morning (starvation level) after several days on a steady mixed diet, it is unnecessary to carry out the series of blood examinations. Cummings and Piness (10), using 0.2 cc. of blood for analysis by the Lewis Benedict method, place more emphasis on the duration of the curve than its maximum height. In diabetes the curve is higher during the second than during the first hour, whereas as we have seen it is the other way in normal subjects. The results of the findings of Humphreys and Williams (63) are plotted in the curves shown in figures 3 and 4. Those in figure 3 are for normal individuals and for a group

that was considered to include very mild cases of diabetes. By comparison of these two sets of curves and considering those given in figure 1 (p. 224), it can scarcely be said that determination of the extent and duration of post-prandial hyperglycemia is a delicate test for incipient diabetes. The curves in figure 4 are from patients with

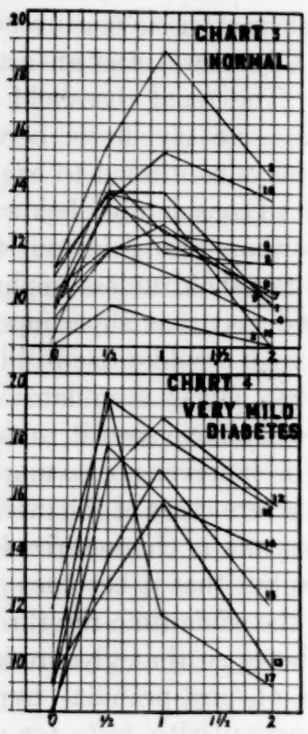

Fig. 3

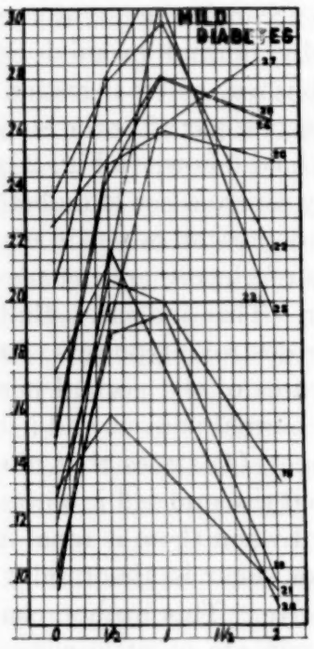

Fig. 4

Fig. 3. Curves of blood sugar following ingestion of 100 grams of glucose in normal individuals, chart 3; and in individuals considered to be suffering from very mild diabetes, chart 4. These curves were compiled from the paper of Williams and Humphreys.

Fig. 4. Blood-sugar curves from decided but mild cases of diabetes; these are on the same scale as the curves in figure 3; compiled from data published by Williams and Humphreys.

decided diabetes and of course the picture is very different although it will be noted that the hyperglycemia is not so markedly prolonged as some have stated it to be in such cases.

It will be remembered that the blood sugar does not rise in a normal person after a carbohydrate-free meal. In diabetics in whom the early morning blood sugar level is not decidedly above 0.17 per cent there

may be a distinct rise after such a diet and the rise is likely to be prolonged. It is evident in about one hour after breakfast but is very slight, if not entirely absent, following the subsequent meals of the day. Indeed the curve may drop in the afternoon and evening even although (carbohydrate-free) food is taken as usual. Very severe cases (initial sugar above 0.17 per cent) yield somewhat different results, for in them non-carbohydrate food does not usually affect the blood sugar; on the contrary, this tends to maintain a (high) constant level throughout the day (44).

Every case showing an abnormally high or prolonged blood-sugar curve or a high starvation level is not necessarily one of diabetes. Similar curves are observed in certain cases of nephritis and in certain diseases of the thyroid and pituitary glands. It is apparently not possible at present to state precisely just what particular type of *nephritis* is associated with the diabetic type of blood-sugar curve and the relationship is still less evident if the sugar content of the urine be alone considered. This is because the renal threshold for sugar often becomes greatly raised in this disease so that no glycosuria may be present as judged by clinical tests, when the blood sugar is far above the normal threshold value. As a general rule, according to Williams and Humphreys (63b), when the nephritis is so far advanced that the nitrogenous metabolites are abnormally high, and uremia is imminent, the blood sugar is also high (but errors in estimation due to excess of creatinine must be avoided). In early stages of the disease when the general metabolism is but little disturbed the blood sugar is usually normal and in cases in which high blood pressure exists without detectable renal involvement the blood sugar levels are slightly higher than normal.

In disease of the thyroid gland the blood sugar may or may not undergo decided variations from the normal. In exophthalmic goiter the postprandial curve is of the diabetic type although the morning blood contains the normal percentage of sugar, the renal threshold being usually little if at all above the normal level, provided there be no kidney involvement (20). Tested by Woodyatt's method, the glucose tolerance was found depressed more or less in proportion to the severity of the symptoms (62a). In depressed functioning of the gland it is commonly stated that sugar metabolism is depressed but this is not invariable (62a). In cases diagnosed as overfunction of the hypophysis, normal types of blood-sugar curve have been found to occur. Mild acromegalia cases, on the other hand, are said sometimes to show

depressed curves (Hamman and Hirschman) but as often they are apparently normal in this regard (Wilder and Sansum).

Further details of the behavior of blood sugar in diseases of the endocrine organs will be found in a paper by Janney and Isaacson (26). We have obviously not attempted to review all of the numerous observations which have been made on the behavior of the blood sugar in disease but only to cite a few typical cases from the more recent literature. This has been done mainly with the object of showing that determinations of the blood-sugar curve cannot be of very great diagnostic value except perhaps in forming an opinion of the severity of the disease in cases of diabetes, or in following the results of treatment, but even in these cases it is probable that careful examination of the urine in relation to food ingestion, as directed by Bailey, is equally valuable. Quantitative determinations of the reducing power of urine from which the disturbing substances have been removed (as by the mercuric nitrate method of Benedict, or by charcoal), appear to offer as useful and as practical a method for the diagnosis of disturbed carbohydrate metabolism as determination of the blood-sugar curve. When abnormally high urinary sugar is found unaccompanied by a fasting hyperglycemia, or other symptoms of diabetes, determination of the blood-sugar curve is however essential in order to determine the renal threshold, for only in this way can it be determined whether the glycuresis is due primarily to a lowering of the renal threshold or to a disturbance in carbohydrate metabolism.

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THE REGULATION OF THE PULMONARY CIRCULATION

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In 1903, Tigerstedt (57) reviewed the then existing literature on the pulmonary circulation and, after a careful evaluation of the separate researches, formulated his conceptions as to its regulation in such a masterful way that his monograph has continued to be the standard reference on the subject. During the eighteen years that have elapsed, however, the study of the pulmonary circulation has been continued. Questions that remained in doubt as well as problems which were apparently solved have been reinvestigated by methods that were well established and by apparatus and technic that is new.

The marvelous development of surgical procedures instituted for the treatment of pulmonary affections and the continued efforts of internists to place the treatment of pulmonary diseases on a rational basis make a survey of the more recent investigations of the fundamental regulatory mechanisms of no less interest to the physician or surgeon than to the physiologist. It shall therefore be our purpose to examine the net results of these recent investigations and decide, if possible, to what extent it is necessary to modify or recast our conceptions as to the control of the pulmonary circulation.

EXPERIMENTAL METHODS EMPLOYED TO STUDY THE PULMONARY CIRCULATION

It is quite obvious that such an end cannot be attained by a mere categorical summary of the often contradictory conclusions reached by different investigators. On the contrary, the results of one set of experiments must be squared with those obtained by other methods, the reason for discrepancies sought and, above all, the worth of the experimental method appraised.

The methods employed to investigate the mechanisms involved in the control of the pulmonary circulation must therefore be briefly considered.

1. Methods involving measurement of pressure changes in the pulmonary vessels or right heart. The mercury manometer has been used to record the mean pulmonary arterial pressure by Airila (1), Dixon and Ransom (16), Erikson (20), Hallion and Nepper (23), Jackson (28), Nolf and Plumier (43), Plumier (45), (46), Petitjean (44), Weber (64) and Wiggers (71). Since slight variations may easily be missed when this instrument is used Cloetta and Anderes (12), Führer and Starling (21), Kuno (33), Schafer (49) and others have therefore substituted saline manometers equipped with special recording systems. Simultaneous records of mean pulmonary and systemic pressures are not in themselves sufficient to interpret the cause of any pressure change. In order to differentiate between "back pressure" effects and active changes in the pulmonary vessels, various investigators have, therefore, recorded the pulmonary venous or left auricular pressures, in addition. The pressures within the left auricle and the pulmonary veins are not necessarily altered in the same direction, however, for, as Wiggers has shown, it is quite possible for the pulmonary venous pressure to fall and the left auricular pressure to rise. Frequently it is also important to determine whether the systolic discharge of the right ventricle has changed, Since this is in part determined by the volume of venous return, mean right auricular pressures have been simultaneously recorded, among others, by Führer and Starling (21), Hallion and Nepper (23), Kuno (33), Langlois and Desbouis (36), Plumier (45), (46). There are conditions, however, when mean pressure observations of auricular and venous pressure are not indicative of changing venous return and consequently cannot be used to gauge variations in the systolic discharge of the right ventricle. Thus it has been found by Wiggers (75) that as long as the return flow is not reduced too greatly, the mean auricular pressure may be maintained by compensatory mechanisms. Wiggers has made use of volume curves taken from the ventricle to study the variations of systolic discharge. This procedure, however, risks the assumption that the output of the two ventricles is always equal; and the method is of course limited to open chest experiments.

Records of mean pulmonary arterial pressures are most conveniently obtained when the chest is opened and the lungs are rhythmically inflated by mild artificial respiration. When it is desirable to determine in what manner the pulmonary circulation is altered in consequence of nerve stimulation or drug administration, or when it is desired to establish the locus operandi, this procedure is not objection-

able. The mistake must not be made, however, of assuming that the same pressures necessarily exist within the intact thorax. Opening of the thorax and institution of artificial respiration involve not only changes in the effective venous filling pressure and possibly also changes in the capacity and resistance of the smaller pulmonary vessels which may modify the reactions of pulmonary circulation, but, in addition, the synchronous influences of the rate and depth of natural respiration cannot be taken into account. In order to derive values representing normal pressure relations within the pulmonary circuit, it is necessary to carry out experiments with the chest closed. Such experiments have been performed by Plumier (45), (46), Schäfer and Lim (49), Wiggers, etc. To accomplish this, the technic first suggested by Fredericq is followed with some modifications. (For details and references cf. Wiggers (72).)

A study of the pulmonary pressures by such methods involves certain annoying features and invites certain criticisms. A larger or smaller lobe of the lungs is necessarily eliminated from the circulation and Kuno's results (33) suggest that, under certain conditions, this may affect the normality of the pressure readings. A serious annoyance exists also in the great tendency of pulmonary blood to coagulate. In order to overcome these objections, Schäfer (49) has recently devised an essentially different method, which is novel in that a specially constructed cannula is inserted through the right ventricular musculature and past the semilunar valves into the mouth of the pulmonary artery; the semilunar valves being allowed to close around the cannula.

Mean pressure measurements, no matter how recorded, are not capable of supplying us with a correct idea as to the pressure fluctuations; practically, it is the pressure recorded by a very inefficient manometer which rarely agrees with the theoretical figure. To record the extremes of pulmonary pressures, maximum and minimum valved manometers have been used (69). Since considerable variation of pressure occurs during the phases of respiration, however, such readings are not equivalent to systolic and diastolic pressures occurring during any cardiac cycle. Furthermore, the mechanisms of valved manometers preclude their use in studying the pulse-pressure variations from beat to beat (78). To obtain such variations of pressures from beat to beat in the intact chest, a special form of pulse-pressure recorder was devised and employed by the writer (69).

On occasion it is desirable to study also the changes taking place in the contour of the pulmonary pressure curves, not only because it is

thereby possible to relate the details of the pulmonary circulation to those of the systemic circuit; but also because, from such records, it is often possible to determine the cause of minor changes in pressures. As in the systemic circuit, this requires optically recording manometers of high vibration frequency (55), (69).

a. The significance of right ventricular pressure. In order to obviate opening of the thorax and the deleterious effects of extensive operative procedures, it has been sought to estimate the pulmonary arterial pressures by introducing a sound through the jugular vein into the right ventricle and connecting it to a recording manometer. The early investigators measured mean pressures only, or determined the maximal and minimal pressures by valved manometers. In the latter way, an estimate of the maximal pressure in the pulmonary artery may be obtained. Ebert (17), Gerhardt (22), Hallion and Nepper (23) and others have recorded right ventricular pressures with the Hürthle membrane or torsion manometer in order to follow variations of pulmonary systolic pressures from beat to beat. Wiggers (74) has pointed out that by recording right intraventricular pressure by optical manometers of high vibration frequency, it is not only possible to follow the pressure changes in the pulmonary artery throughout each systole and to establish the pressures at the beginning of each diastole; but that it is further possible to discern changes in systolic discharge and pulmonary resistance in their contour changes.

b. Pressure studies in the heart-lung preparation. Since the interpretation of pressure curves obtained from the pulmonary system is often rendered difficult by the fact that primary and secondary factors operate at the same time, it has been sought to investigate the pulmonary circuit under conditions in which certain factors can be definitely eliminated or at least controlled. The idea of utilizing a heart-lung preparation for this purpose apparently first suggested itself to Nolf and Plumier (43). Führer and Starling (21), Kuno (33) and, later, Straub (55) adapted the "heart-lung preparation" first described by Patterson and Starling to a study of the pulmonary circulation. In such a system all the mechanical factors capable of affecting the pulmonary circulation (especially venous inflow and systemic resistance) can be controlled or varied while the output of the left ventricle and the pressures in the pulmonary artery, left auricle and systemic arteries can be measured, in selected combinations. While such experiments have been very useful in defining how the circulation *can* be modified under different conditions, it is necessary to emphasize that reactions

so obtained should be transferred to the intact circulation with reserve and caution (cf. Wiggers (73)).

2. Plethysmographic methods. When the internal cavity of a hollow organ (e.g., lung or intestine) enclosed within a plethysmograph communicates with the exterior, a change in the vascular volume may not express itself by a similar change in the plethysmographic volume of the whole organ. A certain amount of expansion may take place inwardly and be lost through the external communications of these cavities. In order to be quite certain that volume changes of the lungs enclosed within a plethysmograph are not dissipated through the bronchi, rather than expressed in plethysmographic records, special technical precautions must be taken.

Two technical procedures have been used: In the method devised by Weber (62) in 1910 and subsequently used by himself and others, the bronchus communicating with the enclosed lobe is ligated while the lung is inflated. In the method devised by Cloetta (9) in 1910, and modified somewhat in work carried out subsequently with his collaborators, the bronchi of enclosed lobes are not ligated; but it is sought either to prevent a volume change through the bronchi by maintaining an equal pressure within the trachea or to evaluate this factor by analyzing the intra-bronchial pressure changes that take place.

The use of these two methods has given results which in many instances are diametrically opposed (13), and hence have led to polemical discussions as to the merits and faults of the two respective methods. Against the use of a ligated lobe to study physiological reactions Anderes and Cloetta (2) have urged the following:

1. A lung lobe placed in a plethysmograph is unavoidably crushed during handling with the consequent collapse of many lung alveoli. With the bronchus ligated no opportunity for re-inflation exists.

2. The enclosed lobe is deprived of its oxygen; and the alveolar CO_2 tension increases. This acts to alter the excitability of its structures and to modify the lung volume and alveolar pressure.

3. The changes in a single ligated lobe may not be typical of reactions in other lobes but may even be passively influenced by them. These investigators are therefore firmly convinced that the method is entirely unsuited for investigating the pulmonary circulation.

Weber (64), in subsequent communications, quite naturally, defends his method against such objections and condemns the method of Cloetta. Categorically stated, he maintains *a*, that CO_2 intoxication and O_2 deprivation are avoided in his method by careful retention of the bron-

chial circulation; and *b*, that alveolar pressure variations do not occur as a result of the gaseous diffusion. He reaffirms his previous position, that volumetric measurements made by Anderes and Cloetta are a mixture of volume effects induced by circulatory changes and those due to broncho-motor action. Weber dissents from the view that changes in lung volumes due to broncho-motor effects can be ruled out even if tracheal pressure does not change. According to him, this merely indicates that the mechanical mechanism keeping the pressure constant functionates properly.

It is apparent that the question as to the correct technical procedure for studying vascular volumes of the lung is still open to further experimentation. At present the relative merits of conflicting results must therefore be based on the character of the accompanying controls rather than on the volume changes themselves. Weber recorded pulmonary volumes and carotid pressure exclusively in his earlier work, believing that by these methods active and passive volume changes could be quite satisfactorily distinguished. Thus, if pulmonary congestion is due to a damming back of blood, he would expect a synchronous increase in lung volume and arterial pressure. If, on the other hand, the congestion results from increased venous return and consequent increase in systolic discharge he would anticipate a delay of 20 seconds or more in the elevation of systemic pressure. Active changes he would distinguish from these passive effects by an entire lack of correspondence between changes of arterial pressure and lung volume. We may conclude with Krogh (32), Cloetta and Anderes (12), and others that experiments of this nature are not sufficiently controlled to distinguish between passive and active congestion. It is true that in a later investigation Weber (64) recorded pulmonary arterial pressures also and thus attempted to refute these contentions but, in most instances, tracings of lung volume and pulmonary pressures were not recorded in the same experiment.

The plethysmographic investigations of Cloetta and his co-workers seem to have been better controlled by simultaneous registration of variations in pulmonary arterial and intratracheal pressure and, when occasion required, by records from other portions of the cardio-vascular system as well. In the last series of experiments, the additional check offered by the varying rate of oxygen absorption was also used. This will be referred to later.

3. Pulmonary blood flow measurements. Methods for determining *the volume flow* and *velocity of blood flow* in the pulmonary circuit are

not only useful in establishing the values for these quantities but are important, also, in interpreting the changes which are produced in the pulmonary circulation by many physiological and pharmacological influences.

a. Pulmonary volume flow and its significance. Variations in the volume flow of pulmonary blood in the intact circulation have been studied by two methods:

Wiggers (67), (71) devised and used an apparatus by which the flow of blood from a peripheral end of a pulmonary vein or the flow from a cut in the lung itself can be continuously recorded. The chief objection to the method is, of course, the progressive loss of blood—but, if tests are made with expedition, many valuable data may be obtained before the circulation is seriously affected.

A second method is based on the following premises: Since arterial blood is practically saturated with oxygen at all times, the alveolar oxygen absorption rate can vary only with the volume of blood passing through the pulmonary vessels, as long as general metabolism is unaffected. Consequently, *if the lung volume remains unaltered,* any change in the recorded rate of oxygen absorption during short intervals of time is an index of pulmonary blood flow. In applying this principle to the study of the pulmonary circulation, Anderes and Cloetta (2) devised an apparatus and so arranged their experiments that the recorded intratracheal pressures varied inversely with the absorption rate of oxygen. As the lung volumes changed during the course of these experiments, Anderes and Cloetta attempted to differentiate possible changes in intratracheal pressure, due to passive congestion or broncho-constriction, by simultaneously recording pulmonary arterial pressure and lung volumes. Both the principle of the method and its application by Anderes and Cloetta have been criticised (64), (56). Straub points out, for instance, that the fundamental assumptions upon which the method rests are not valid: neither the general cell metabolism nor the oxygen capacity of the venous blood being constant under the conditions of the experiments.

Pulmonary circulation-time: An estimate of the velocity with which blood passes through the pulmonary vessels may be gained from a study of the pulmonary circulation-time. Plumier (45) determined this interval by estimating the time required between decompression of a previously compressed vena cava and the consequent maximal rise of arterial pressure. The method of Stewart (53) was employed by Edmunds (18) and with slight modifications by Langlois and Desbouis (36).

Stewart (53) has clearly analyzed the deductions that may reasonably be drawn from experiments in which the pulmonary circulation-time changes. As stated by him, the circulation-time varies directly as the capacity of the pulmonary blood stream at the beginning of the observation and inversely as the minute volume discharged by the right ventricle. Since the former factor may be altered by variations in the pulmonary resistance and the latter by changes in heart rate or systolic discharge, it follows that an increased circulation-time, for instance, merely means that, in proportion to the minute volume discharged by the right ventricle, the pulmonary resistance is relatively high. A change in either or both factors may be the cause of the altered circulation-time. It is conceivable, also, that when one factor operates intensely, the other factor may work in an opposite direction and yet the predominant and overpowering influence of the first lead to an increased circulation-time. The measurement of the pulmonary circulation-time and of its variations is, therefore, an excellent criterion as to how the factors balance one another under different conditions. If, however, it is desired to use the method as an index of vascular contraction in the pulmonary system, it is necessary to be quite certain that the minute output of the right heart has not altered at all or that it has changed in the reverse direction.

After demonstrating that a condition of augmented pulmonary resistance exists, we are still not in a position to state that this indicates increased constriction. The total resistance in an organ or circuit is not entirely controlled *a*, by the degree of arteriole constriction but is also modified by *b*, the caliber of the capillaries; *c*, the "head on" pressure in the veins draining the capillaries; *d*, variations in extravascular support; and *e*, the viscosity of blood. Of these factors the third at least must be carefully controlled in pulmonary circulation experiments.

4. Perfusion methods. In order to determine whether nerves or chemical influences produce active changes in the caliber of the smaller arterioles (and capillaries?) the rhythmically inflated lungs have been perfused and the outflow from the pulmonary veins or from the left auricle estimated. As a perfusion fluid, Baehr and Pick, Campbell (7), Beresin (4) and Wiggers (68) employed Locke's or Tyrode's solution. To retard the rapid onset of edema, Brodie and Dixon (6), Führer and Starling (21), Plumier (46) and Tribe (60) employed defibrinated blood. Schafer and Lim (49) added 6 per cent gum arabic to the perfusing fluid. Wiggers (68), in special experiments, employed gelatin for similar purposes.

In evaluating the effect of drugs on the pulmonary vessels by the perfusion method, certain technical errors must be guarded against by attention to the following details:

1. Owing to the relatively low resistance in the peripheral pulmonary vessels, it is important that the injection proceed without consequential changes in the perfusion pressure and that the drugs be dissolved in a menstruum having the same viscosity as that of the perfusion fluid (68), (49).

2. In order to detect temporary changes in outflow, it is important, if small changes are not to be obscured, that the outflow rate be continuously recorded (67).

3. In order to guard against the possibility that changes in venous outflow may not accompany vasomotor effects, the rate of arterial inflow should be simultaneously gauged. Vasomotor reactions occurring in the arterioles must always diminish the volume of blood passing through the capillaries into the veins. If, however, the venous channels are comparatively capacious they may accommodate slightly changing inflow volumes from the capillaries without affecting the venous outflow from a cannula. This was clearly demonstrated by Wiggers (67) when minor vascular changes took place in the renal vessels and probably plays a considerable part in pulmonary perfusion experiments—e pecially in those in which the capacious left auricle is added to the venous reservoirs. Wiggers (68) has therefore suggested the use of the diastolic pressure variations as a control. This may be accomplished in such a way that, during the opening of a stop cock, the organ is supplied by a constant systolic pressure maintained by a "constant-pressure device" and, during subsequent closure of the stopcock, the organ is fed by the pressure in the peripheral tubes. Under these conditions, the rate of what may be termed the diastolic pressure-decline and the height of the diastolic pressure itself are solely determined by the resistance in the perfused organ. Under certain conditions such a criterion is far more sensitive in recording minor variations in vascular resistance than the venous outflow.

5. Methods designed to test the reaction of isolated pulmonary rings. The method first devised by Meyer (41) for studying the contraction of arterial rings has been employed to test the reaction of pulmonary vessels to drugs. This very simple method consists essentially in removing, post mortem, a segment of artery from a vessel of considerable size, mounting the ring in a receptacle containing Ringer's, Locke's or Tyrode's solution or defibrinated blood. The arterial ring is con-

nected to a delicate lever in such a way that it is slightly stretched. This method has been used by Barbour (3), Campbell (7), Cow (15) and Langendorff (35) as well as by Meyer in studying the reaction of the pulmonary vessels. Rings of pulmonary vessels taken from the ox, calf, sheep, pig, rabbit, cat, man and monkey have been studied.

Positive results thus obtained are of definite value. Similar importance cannot always be attached to negative results, however. The criticism has been made that the vessels are obviously studied under unnatural conditions and may conceivably react differently than the normal vessels (13); or the reactions may be too feeble to move a ponderable lever writing with friction on a smoked surface (49).

Even if the reliability of the method remains unquestioned it should always be borne in mind that large vessels may not react in the same way as the smaller arterioles of the same system. It is quite conceivable that the larger vessels supplied with a relatively smaller bulk of muscle fibers may fail to react visibly when the arterioles, which are especially endowed with contractile elements, show a definite contraction.

THE NORMAL PRESSURE VARIATIONS AND BLOOD CONTENT OF THE PULMONARY CIRCUIT

Tigerstedt (57) has summarized the mean pressure readings obtained by numerous investigators from the exposed pulmonary artery. According to his tabulations, the mean pressure varies considerably in different animals: averaging 20 mm. Hg. in the dog, 18 mm. Hg. in the cat and 12 mm. Hg. in the rabbit. Values more recently reported by Erikson (20) and Führer and Starling (21) apparently agree with these earlier data. Plumier (45) and Schafer (49) both direct attention to the marked variation of mean pressure occurring during each act of respiration when the chest is intact. Such readings of mean pressure give us, however, a very imperfect idea both as to the extent and the character of the pressure fluctuations in the pulmonary arteries. Wiggers (69) found, for example, that in the closed chest the maximal pressure fluctuates between 60 and 32 mm. Hg. (average 43.9 mm.) while the minimal pressures range from 6 to 21 mm. Hg. (average 11.9 mm.). Since these figures express only the highest systolic pressure reached during expiration and the lowest diastolic pressure during inspiration, they also do not permit a fundamental analysis of the pressure variations. This can, in fact, be accomplished only by follow-

ing the pressure change from beat to beat. When this is done by a special pulse-pressure apparatus, it is found that the actual pulse-pressure during any cardiac beat is much less than the difference between maximal and minimal pressures. This is due to the fact that while both systolic and diastolic pressures fall during inspiration and rise during expiration, the pulse-pressures as a rule are greater during the latter phase.

Both the average systolic and diastolic pressures, as well as the maximal and minimal pressures, are maintained at their normal level only when the subsidiary force or normal respiration is acting. Thus, during apnea, the average systolic as well as the maximum pressure is lower, while the average diastolic and minimal pressures are higher. During dyspnea the reverse effects obtain.

During each cardiac cycle a small oscillation is apparently superimposed on respiratory variations of mean blood pressure curves. When registered by optically recording manometers, each of these cardiac variations is found to consist of a characteristic pressure pulse with a contour resembling that described by Frank in the systemic circuit (cf. Straub (55), Wiggers (69)). The details of these pressure pulses differ somewhat during inspiration and expiration. During inspiration the auricular wave is less prominent, but the amplitude of the preliminary vibrations occurring during the isometric phase of systole increases. The primary oscillations become sharper and more spike-like indicating that a greater throw and rebound of the blood column occurs during this phase. The systolic summit which rapidly rises to a sharp peak during expiration approximates a short ascendng or horizontal plateau during inspiration. Systolic and diastolic pressures fall during inspiration and rise during expiration.

The pressure variations in the pulmonary veins have been little investigated in the closed chest. The earlier results of Plumier and Wiggers show that the mean pressure is little above zero. Probably the pulmonary venous pressures do not exceed greatly those in the left auricle. The writer found that the mean left auricular pressure is usually negative during normal inspiration (-2 to 50 mm. saline) but becomes positive during normal expiration ($+$ 6 to $+$ 38 mm. saline). The effective pressure, i.e., the difference between left auricular and left intrathoracic pressure, is slightly greater during inspiration (51.5 mm. saline) than during expiration (46.4 mm. saline).

How is the great drop in pressure gradient between pulmonary artery and left auricle indicated by these results and specifically emphasized,

also, by Führer and Starling (21), to be explained? The pressure in the short pulmonary venous trunks and left auricle is determined not only by the blood volumes entering by way of the capillaries, but also by the amount withdrawn from them by the left heart. The relatively low venous pressure must therefore indicate that the left ventricle keeps the pulmonary vessels well pumped out. As a result the left heart, unlike the right, does not enjoy a luxus supply of venous blood, but its continued function is conditioned at all times upon the receipt of an adequate supply of blood through the pulmonary capillaries.

We may briefly inquire how this squares with data as to the blood content of the lungs. Experimental results by Menicanti (40), Spehl and Desquin (51) and others indicate that the lungs contain only 5.3 to 9 per cent of the total blood volume of the body. During a vigorous circulation Kuno (34) found that this might increase to a maximum of 19.4 per cent. No assurance is given, however, that these figures apply to the intact circulation. Since less than half of this volume is probably contained in the pulmonary veins, it is evident that they contain a much smaller reserve volume than the systemic veins supplying the right heart (32).

THE MECHANICAL FACTORS CONCERNED IN THE DYNAMICS OF THE PULMONARY CIRCULATION

Three mechanical factors, operating separately or together, may conceivably alter the pressures and volumes of blood contained in the pulmonary vessels. They are *1*, the minute output of the right ventricle; *2*, the resistance and capacity changes in the pulmonary circuit; *3*, "back-pressure resistance" produced in the left heart by changes in the systemic circuit.

1. The minute output of the right heart. The minute volume discharge from the right ventricle into the pulmonary artery is determined by the heart rate and systolic discharge.

a. Effect of systolic discharge. A great deal of experimental work has accumulated to show that at constant heart rates the systolic discharge depends on the venous return. The experiments of Henderson and his collaborators (24) indicate that this concerns a reduction of venous return below normal alone; while the arguments of Krogh (32) and experimental work of Starling and collaborators (52), Straub (54), Socin (50), as well as Wiggers (70), indicate that this also follows an increased venous return. As relating to the pulmonary circulation we

may refer first to the work of Plumier (45) who in 1904 demonstrated that compression of the inferior vena cava causes a reduction in mean pulmonary arterial pressure. More recently, Straub (56) has shown that such a reduction of venous inflow causes in the heart-lung preparation a decreased systolic discharge, decreased lung volume and decreased left auricular pressure. Saline infusion, by augmenting the systolic discharge, on the contrary, increases the mean pulmonary arterial pressure as has been shown by Erikson (20), Anderes and Cloetta (2), and Cloetta and Staubli (14) and others. Accompanying the increase in pulmonary arterial pressure, Cloetta and his co-workers found an increase in the plethysmographic lung volume and an increased rate of oxygen absorption, facts which they interpret to indicate an active pulmonary congestion accompanied by a better blood flow through the lungs. The increased discharge of the left heart, secondarily induced, has generally been found to cause less elevation of systemic than pulmonary pressure so that the ratios of pulmonary to systemic mean pressures are changed. Führer and Starling (21), however, found, in their heart-lung preparation, a corresponding increase in both pressures—the normal pressure ratio always remaining approximately 1:6. Results obtained on a similar heart-lung preparation by Straub (54) do not bear this out, however. He was unable to discover any effect of increased venous return on either the initial or maximum pressure within the left ventricle.

There is obviously a limit beyond which the right ventricle is unable to expel all the returned blood, with the result that it dilates and pulmonary arterial pressure falls. This is shown by the experiments of Kuno (33), who found that a very considerable increase in venous inflow always causes an increase of pressure in the pulmonary artery, left auricle and aorta even if the systemic arterial load is not reduced by changing the controllable artificial resistance of his heart-lung preparation. In such cases, right auricular pressure is also elevated but Kuno's results indicate that the relative elevation of the right auricular and pulmonary arterial pressures depends on the inflow rate previous to its augmentation. Thus, if the inflow rate is small at the start, the right ventricle is capable of taking care of increasing venous return, as evidenced by a relatively smaller elevation of the venous than of the pulmonary pressure. If, however, the previous inflow rate is already large, then every additional increase in inflow causes comparatively little additional elevation of pulmonary arterial and left auricular pressures but a great increase of the pressures in the

right heart, i.e., the heart is decompensated. The experiments of Kuno show further that the natural support offered the ventricles by the pericardium is an important factor in delaying decompensation. Thus, he found that if the pericardium is opened while a small or moderate inflow takes place into the right heart, the right ventricle tends to dilate and the pressures in the pulmonary artery and right auricle decline. Within 20 seconds, however, the pulmonary arterial pressure increases again to or above normal, while the right auricular pressure slightly rises. The results are different when the pericardium is opened while the heart is receiving a large inflow; the dilatation of the right heart and fall of pulmonary pressure are then reported to be permanent.

That similar effects also occur in the pulmonary arterial system when the chest is intact, is indicated by the variations of the second pulmonic sound during saline infusion. The writer (77) has recently reported that, when saline is injected to the point where the heart becomes irregular and the intensity of the first sound decreases, then the intensity of the pulmonary second sound also diminishes. If injection is stopped and the heart is allowed to recover, the second pulmonary sound becomes louder and louder, reaching an intensity much in excess of normal. This has been interpreted to indicate that, during extreme dilatation, the pressure at the onset of diastole falls when the heart is much dilated but rises when it recovers from such dilatation.

The conclusions may therefore be reached that the pressures throughout the pulmonary circuit and in the left auricle vary directly with the systolic discharge of the right ventricle, provided, of course, that other factors remain equal and that the increased return is not sufficient to cause dilatation and decompensation.

b. Changes in heart rate. An alteration in heart rate obviously affects the minute discharge of the right heart and may at once be looked upon as a factor controlling the pulmonary arterial pressures. Since the minute discharge of the left heart is presumably affected to an equal degree, however, we may theorize that the total blood within the lungs must remain unchanged. The plethysmographic experiments of Weber (62) as well as those of Anderes and Cloetta (2) indicate, however, that an increase in lung volume actually takes place when the heart is slowed. The latter investigators and also Erikson (20) found that the mean pulmonary arterial pressure falls. From this we may conclude that the volume of pulmonary venous blood increases while that contained in the pulmonary arteries decreases.

The influence which changes in heart rate have on the pulmonary systolic and diastolic pressures was studied in a large range of rates by the writer (69). The results show that, as the heart cycle increases in length up to 0.8 second (approximately), the systolic pressure either undergoes no change or displays a slight tendency to increase. When the cycles exceed 1 second in length, the systolic pressure actually increases. Pari passu with these changes the diastolic pressure undergoes a reduction. These studies are of interest in connection with the rhythmic variations occurring naturally during inspiration and expiration for it is found that, within the ranges that these variations usually occur in man (0.6 to 0.9 second) there is practically no effect on the diastolic and a very slight effect on the systolic pressure.

2. The resistance in the pulmonary circuit. The startling observation of Lichtheim that ligation of one entire lung may be without effect on the systemic pressure inclined Tigerstedt (59) to question whether mechanical variations in resistance, such as occur, for instance, during respiration, can have any profound effect on the pulmonary arterial pressure or on the blood flow through the lungs. The observations of Lichtheim were confirmed by Plumier (45) and by Gerhardt (22), who found that ligation of the left pulmonary artery did not permanently affect the carotid mean pressure. R. Tigerstedt (58), in 1907, corroborated and extended the observations by showing that the minute output of the left heart, as measured by the strohmuhr, was only slightly decreased. These experiments are important in demonstrating that compensatory vasoconstriction is not the cause of the maintained arterial pressure, but that, as he had previously suggested, the flow returned to the left heart is maintained at practically a normal level through the opening of new channels in the lungs.

Observations which indicate that changes in pulmonary resistance play an important part in the control of pulmonary arterial pressures were reported by the writer (74) in 1914. In my experiments, the right ventricular pressure curves showed not only an elevation of the systolic pressure after compression of a pulmonary branch of a right lobe, but also such changes as are usually regarded characteristic of an increased arterial resistance. The ascending limb of the right intraventricular pressure curve increases in height, reaches its summit later and the pressure-maximum occurs later during ejection. More recently Straub (55), using similar methods, states that he was unable to confirm these findings and attributes the phenomena obtained by myself to variations in systolic discharge accidentally produced in manipula-

tion. No records of the actual effects obtained are published by Straub however. In 1915 the question was studied by Kuno (33) on a heart-lung preparation. He found that if the venous inflow is small, elimination of one lung causes only a very slight and temporary fall of carotid pressure but a permanent increase in pulmonary arterial pressure. If the venous inflow is large, however, pulmonary arterial pressure rises greatly after occlusion of a pulmonary branch while the left auricular and aortic pressures are permanently reduced. Kuno therefore believes that the contrary results obtained by previous workers are characteristic only when the venous return is low; and warns us that, from such results, generalizations should not be made and applied to normal animals in which the venous flow is much larger.

In conclusion, we may believe that the effects produced by mechanical changes in lung resistance are capable of affecting the pulmonary arterial pressures and the pressure variations in the right ventricle. Indeed it is probably through such a pressure elevation that a normal flow through newly opened circuits is maintained.

The influence of inspiration and expiration on the pulmonary resistance has been studied in several ways. Perfusion of the lung vessels has been a favorite method of investigating the influence of inflation produced by both positive pressure and negative suction. This work, carefully reviewed by R. Tigerstedt (57), shows that the flow through the lungs increases during inspiration. Clamping the roots of the lung at the end of expiration and inspiration has been found unsatisfactory, for, aside from the fact that the results are discordant, the method does not distinguish variations in blood content due to an altered output from those due to a change in the vessels themselves. Histological examinations of collapsed and inflated lungs are reported by Poiseuille to show that the lung capillaries are longer and narrower,—findings corroborated by Cloetta (10). Continuing his investigations, Cloetta (11) subsequently pointed out that two opposite forces act upon the intrapulmonary vessels when the lungs expand: *1*, A radial traction of the expanding alveoli which tends to enlarge the vessels between them; but this force is soon converted into an actual compression when the alveoli acquire the polygonal shape of inspiration. *2*, A linear traction which lengthens the vessels and thereby reduces their caliber. The conclusion is reached from these histological studies that the forces causing an increased resistance during lung expansion always more than counterbalance the dilating influence.

Cloetta also substantiated these deductions by enclosing a lung within a plethysmograph. When the lungs were inflated by a negative pressure, the lung pulsations from the plethysmograph decreased, the systemic pressure fell and the pulmonary arterial pressure rose. These observations were interpreted as showing that, when the lungs are inflated, the resistance within the pulmonary system increases. Upon such an hypothesis, it would be difficult, however, to explain the fall of pulmonary arterial pressure during natural inspiration. Cloetta has carried his work still farther and showed that, if the lungs within a plethysmograph are only partially inflated, both pulmonary and systemic arterial pressures fall. The former fact is interpreted as indicating that, when the lungs are only partially inflated, the dilating influence of radial traction becomes supreme and the lungs are in the most favorable condition for a larger blood flow. Consequently, as applied to the natural influence of inspiration, Cloetta's modified views are that the intrapulmonary vessels are mechanically dilated at the beginning of inspiration but tend to be compressed toward the end of this respiratory phase.

It should be borne in mind, however, that the entire pulmonary resistance is not determined by the size of the smaller intrapulmonary vessels alone. de Jager (27), long ago, supplied interesting evidence as to the effect of negative pressures on the extrapulmonary vessels. He showed that, when both the pulmonary artery and vein were submitted to the same negative pressure the vein, which was thinner walled, dilated, while the arterial diameter decreased. Apparently this occurs because the dilatation of the vein lessens the venous pressure which, by diminishing the "vis a fronte," increases the flow from artery to vein and consequently reduces the pressure and caliber of the artery. According to this observation—which has, to the writer's knowledge, never been repeated—the caliber of the pulmonary vessels depends partly on external and partly on internal pressures of the arteries. It is conceivable that a similar decrease in the "vis a fronte" may be brought about by a dilatation of the auricle or, even as Lewis (38) suggests, by an increased filling of the left ventricle due to a more negative pericardial pressure.

It is evident that a change in the total resistance within the pulmonary circuit is the resultant of *a*, a changing capacity of the extra and intrapulmonary arteries and branches; *b*, the changing resistance of the smaller arterioles and capillaries, and *c*, the changing venous and left auricular pressures.

3. Back-pressure effects. If, even for a few beats, the minute discharge of the left heart is reduced while that of the right heart remains unaltered, a stasis of blood within the pulmonary veins must take place. By offering greater resistance to the normal flow of capillary blood this increased "vis a fronte" tends to elevate the pulmonary arterial and right ventricular pressures, also. This dynamic sequence is implied by the term "back-pressure effects."

How frequently does such a "back-pressure effect" occur when the arterial load is increased? The earlier experimental work on the subject was contradictory. Thus Welch (65) in his classical experiments found that ligation of the aorta in rabbits produces a considerable elevation of pulmonary arterial pressure leading eventually to pulmonary edema. Bradford and Dean (5) investigated the effects of such changes in arterial resistance as more probably come within the range of possibility within the intact circulation. They found that temporary compression of the aorta or increased vasoconstriction causes only a slight and inconsequential elevation of pulmonary arterial pressures. The tendency has therefore been to conclude with Hill (26) that such "back-pressure effects" follow increased arterial resistance only when the heart muscle is intrinsically depressed.

More recent experiments have concerned themselves with the two distinct questions: *1*, as to whether there is a retention of blood in the left ventricle, left auricle and pulmonary veins; and *2*, whether such a retention can cause an elevation of pulmonary arterial pressures as well. The degree of pressure elevation, to a certain extent, determines whether a passive congestion of the pulmonary veins takes place. Thus, it appears that if the pressure is moderately elevated by peripheral vasoconstrictor action, induced either by splanchnic stimulation (59) or mild epinephrin constriction (58), there is no reduction in the minute volume discharged by the left heart. If, however, as R. Tigerstedt (58) has shown, the resistance increases greatly after larger doses of epinephrin then the output is reduced, and presumably passive congestion obtains. This has been confirmed by Velich (61) who found that, under these conditions, the left auricular and pulmonary arterial pressures also increase. It is probable, however, that in such cases other factors than the primary increase in arterial pressure may be concerned. Thus, Krogh (32) points out that the effect may possibly be in part ascribed to a deleterious action of the very high arterial pressures on the heart. The experiments of Plumier (46) indicate, furthermore, that these results may possibly be explained by the slowing of

the heart. He found that when the slowing of the ventricle is prevented by previous vagus section, epinephrin always causes a fall of left auricular pressure.

Führer and Starling (21), working with a heart-lung preparation in which cardiac rate and venous inflow were controlled, found that, in apparently vigorous hearts, every elevation of systemic pressure causes a corresponding rise of pressure in the left auricle, pulmonary artery and even in the right auricle. Cloetta and Staubli (14) found that compression of the thoracic aorta always induces an increased lung volume and some elevation of pulmonary arterial pressure. On the other hand, Modrakowski (42) reports that marked passive pulmonary venous congestion produced by blocking the pulmonary veins does not affect pulmonary arterial pressure. Straub (56), who also used a heart-lung preparation, found that an increased arterial resistance always produces a passive pulmonary congestion as indicated by an increased lung volume and increased left auricular pressure but these changes according to him do not affect the pulmonary arterial or right ventricular pressures as long as the heart has a good blood supply at the start. Similar conclusions are reached on less adequate experimental grounds by Gerhardt (22).

While such experimental observations leave no doubt that a marked increase in the arterial resistance causes a retention of blood within the left heart leading to a passive pulmonary congestion, they are not concordant on the question as to whether this is also capable of affecting pulmonary arterial pressures. Probably these contradictory results are in part explainable on the basis of differences in apparatus and technical procedures employed, but a careful consideration gives the impression that the effect on pulmonary arterial pressures is determined by the operation of certain compensatory reactions which will be analyzed later.

THE NERVOUS CONTROL OF THE PULMONARY VESSELS

1. The effects of nerve stimulation. Direct experimental evidence as to the existence of a nervous control of the pulmonary vessels has been somewhat contradictory. Brodie and Dixon (6), in 1904, could find no alteration in the flow through the lungs perfused in situ upon stimulation of either the sympathetic or vagus nerves. In the same year, Plumier (45) reported that stimulation of certain sympathetic fibers causes an increase in pulmonary arterial and a drop of left auricular

pressure. In a second communication, he also reported a diminished flow in perfused lungs when the annulus of Vieussens was stimulated. Erikson (20), in 1907, obtained only negative effects on pulmonary arterial pressures upon stimulation of the vagus fibers, after atropin had previously been administered. Although the pulmonary arterial pressure increased after stimulation of various portions of the thoracic sympathetic chains and heart rate variations could be excluded, the fact that the systemic pressure also augmented points to the probability that augmenting cardiac fibers might have induced the results.

Positive evidence that the vago-sympathetic nerve of the turtle contains pulmonary vasoconstrictors was adduced by Krogh (31), who found that the pulmonary blood flow decreases during vagus stimulation and increases after vagus section. These changes were accompanied by corresponding changes in oxygen consumption. In the same year Weber (62) was unable, however, to detect any volumetric variations in the lungs of cats that could be attributed to nerve stimulation. His criteria may, however, be questioned. In 1911, Karsner (29) found histological evidence of nerve fibrils in the media of the pulmonary artery. Whether they were sensory or motor in character could, of course, not be determined. Very recently, O. Larsell (37) in work as yet unpublished has succeeded in tracing nerve fibrils directly to the muscle elements in the pulmonary arterioles of rabbits. At the 1920 meeting of the American Physiological Society, Carlson and Luckhardt (8) demonstrated a contraction of the pulmonary artery in the frog when the vagus nerve was stimulated. The diminution in the size of the pulmonary artery persisted when vagus effects on the heart were abolished by the use of nicotine but failed to occur after atropin—which is thereby shown to paralyze the vasomotor endings in the lungs. On the basis of such evidence, we may conclude with Schafer "that the pulmonary system is provided with vasomotor nerves can no longer admit of doubt."

2. The reaction of the pulmonary vessels to epinephrin. As a result of Elliot's (19) investigations, the reaction of blood vessels to epinephrin has come to be regarded as a convenient criterion as to the existence of vasomotor fibers; for even if a constrictor reaction to epinephrin be not invariably accepted as quite certain demonstration of a nerve control, the lack of such a reaction supplies presumptive evidence that probably such a control does not exist. The extensive work as to the effect of epinephrin on the pulmonary vessels is best grouped about the method used to investigate its action.

Many investigators have sought to find evidence of a constrictor action by studying its effect on the intact pulmonary circulation. Cybulski and Symonowicz first demonstrated that adrenalin slightly elevates the pulmonary arterial pressure, but since Velich (61) later showed that the pressure in the left auricle also rises, it became doubtful whether a rise of pulmonary arterial pressure alone may be considered evidence of a constriction of the lung arterioles. In 1904 Plumier (46) showed that the backing up of blood which causes a rise of left auricular pressure in such cases is due to a slowing of the heart and can be prevented by the section of the vagi nerves. Adrenalin then causes a rise of pulmonary arterial pressure, while the pressure in the left auricle actually falls. Having thus ruled out "back-pressure effects," Plumier interpreted his reactions as due to a constriction of the pulmonary vessels. These results have since been confirmed by Petitjean (44) and myself (71).

On carrying my experiments further, however, an obstacle to such an explanation arose, for it was found that the outflow and pressure recorded from the peripheral end of a pulmonary vein were always increased by adrenalin, whereas, had a constriction alone occurred, they should have decreased. The fact is that section of the vagi nerves does not abolish the action of adrenalin on the heart, for, though changes in rate may not be apparent, it still tends to augment the minute output from the ventricles. Consequently, the right ventricle throws more blood into the pulmonary arteries (as shown by the greater outflow from a pulmonary artery) and so causes a rise of pulmonary arterial pressure. This greater amount is partly transferred through the capillaries into the pulmonary veins and thus increases the pressure and flow from the peripheral end of the latter. The fall of pressure in the left auricle is probably produced by the more complete draining into the left ventricle consequent to the greater relaxation induced by adrenalin.

More recently the question has been reinvestigated with modifications and innovations in technic and methods. In 1910 Weber (62) obtained first a decrease and then an increase in lung volume indicating, as he believed, a primary vasoconstriction which is secondarily overbalanced by passive congestion. This was not confirmed, however, either in plethysmographic experiments of Cloetta and Anderes (12), or in the experiments of Kraus (30) and Retzlaff (48) who both consistently recorded an increase in pulmonary volume after epinephrin even when the vagi nerves had previously been sectioned. Subse-

quently, Anderes and Cloetta (2) further showed that these changes are accompanied by an increased rate of oxygen absorption which they interpret as conclusively precluding active vasoconstriction. The results are exactly in accord with my own experiments alluded to above but it does not seem clear why the alternative conclusion may not be drawn, viz., that any constriction which may be induced is overpowered by the increased minute discharge of the right heart.

In 1913 Dixon and Ransom (16) noticed that the elevation of pulmonary arterial pressure precedes that in the systemic circuit, while the rise of pulmonary venous pressure is delayed from 5 to 10 seconds. They drew no conclusions as to its significance, however. More extensive observations upon the relative onset of pressure changes in the pulmonary and systemic circuits were made by Schäfer and Lim (49) in 1919. These investigators analyze the many factors which may secondarily affect pulmonary arterial pressure during action of epinephrin and which may cause varied effects in different animals. Their chief evidence that epinephrin constricts the pulmonary vessels apparently rests on the observation that in some experiments intravenous injection affects the pulmonary arterial pressure before the systemic if the drug is administered intravenously, while the systemic effects precede the pulmonary if it is injected directly into the arterial circuit. In spite of an elaborate discussion of the dynamics involved, it is not clear why the primary effect on the pulmonary circuit might not be attributed to an initial effect on the right ventricle rather than on the pulmonary vessels.

In 1913 Führer and Starling (21) studied the effect of epinephrin on the pulmonary circuit in the heart-lung preparation, in which all factors are supposedly under control. They obtained a rise of pulmonary arterial and a fall of left auricular pressures. That the latter could not be attributed to a stronger contraction of the left ventricle was indicated by the observations that the output of the left ventricle was not increased but, in fact, often diminished. It was not shown, however, that the suggestion which the writer had previously made was not concerned, viz., that as a result of the greater diastolic relaxation induced by epinephrin more blood might not be drained and retained by the left ventricle.

In conclusion,—while a number of investigators have obtained results which to them appeared to indicate clearly that epinephrin constricts the pulmonary vessels, the writer feels that the conclusions reached in 1909 still apply. As the writer (68) distinctly emphasized,

these results do not indicate that adrenalin is without action on the pulmonary vessels, or dilates them. They do indicate, however, that if any action exists, it is passively overpowered by the simultaneous effect of the drug on the heart. For this reason the method can shed no light on the fundamental question as to whether or not the pulmonary vessels are actively affected by adrenalin.

We may next consider the results obtained by the perfusion method. Brodie and Dixon (6) in 1904 found no effect or a slight tendency to dilatation—as indicated by the rate of venous outflow. Plumier (46) in the same year, using the same method, found a definite decrease in venous outflow which he attributed to vasoconstriction. This was confirmed by Wiggers (68) in 1909. At that time the writer pointed out that the dilator effects of Brodie and Dixon might be only apparent and really due to a reduction in the viscosity of the perfusate which resulted when adrenalin dissolved in Locke's solution was added to the perfused defibrinated blood. Similar evidences of a constrictor effect by the perfusion method have been subsequently obtained by Campbell (7), Führer and Starling (21), Tribe (60), Schafer and Lim (49). Baehr and Pick as well as Beresin (4), on the other hand, report negative results.

The effect of epinephrin has also been tested on isolated strips of pulmonary artery. Meyer (41) in 1906 first presented evidence that pulmonary rings taken from the ox are constricted. These observations have since been confirmed by Langendorff (35), Campbell (7), Cow (15), Barbour (3) and Macht (39), in the case of pulmonary rings taken from many different animals, man included. The latter investigators noted, however, that the contractions become less and less as the smaller vessels are approached, finally failing entirely in the smaller rings examined. Cow concludes from this that the sympathetic innervation is limited to the larger pulmonary vessels. As Schafer and Lim well point out, however, this may readily be attributed to the fact that the smaller vessels do not contract sufficiently to affect the ponderable levers which were employed.

It is obvious from such a review that, while a few reports are negative as regards the reaction of the pulmonary vessels to epinephrin, a critical estimate of the work leads to the conclusion that epinephrin does constrict the pulmonary vessels and that this in turn may be taken as supporting evidence of their nerve control.

3. Reflex vasomotor changes. That the pulmonary vessels possess a vasomotor control is indicated by *a*, the discovery of nerve fibers in the

vessels; *b*, by their reaction to direct nerve stimulation; and *c*, the reaction of these vessels to epinephrin. These experiments indicate also that as compared with other organs the vasomotor reaction in mammals is comparatively feeble and readily overpowered by changes in the minute discharge of the right heart or by "back-pressure effects" from the systemic side of the circulation.

It is of distinct physiological interest, therefore, to inquire whether they are ever reflexly excited and whether such a vascular reaction plays an important rôle in the control of the pulmonary circulation or whether, in the pulmonary as the cerebral vessels, they are of questionable significance.

The earlier work has been reviewed by Tigerstedt (57) and Hill (26). Plumier in 1904 (45) tested the reflex effects of inhaled ammonia and formalin vapors on the pulmonary circulation. This caused a fall of pulmonary and aortic arterial pressures probably due, as Plumier points out, to a reflex cardiac slowing. No indications were obtained that the pulmonary vessels were reflexly affected. Weber (62) in 1910 found no reflex vascular changes as estimated by changes in the lung volume either from inhalation of ammonia or by stimulation of the sciatic and crural nerves. Excitation of the central vagus nerve, however, caused an increase in lung volume from which he felt justified in deducing a reflex pulmonary constriction. Passive changes were, however, not clearly eliminated. Langlois and Debouis (36) found that stimulation of the central end of a vagus nerve increased the pulmonary circulation-time from a normal value of 7 seconds to 9 seconds. Since he found also an increase in pulmonary arterial pressure and an increased right auricular pressure, as in the case of epinephrin injections, he concluded that this gave evidence of reflex vasoconstriction. That this may not be unreservedly accepted as conclusive was pointed out earlier in the review.

More recently Schafer (49) adduced what to him seemed evidence that the pulmonary vessels are tonically constricted and may be reflexly dilated by stimulation of the depressor nerve in rabbits. He found, in animals with vagi previously sectioned (to prevent reflex slowing), that the pulmonary arterial as well as the systemic pressure fell in the closed chest from stimulation of the depressor nerve. Reasoning that through dilatation of systemic vessels the right auricular pressure and systolic discharge is probably increased under these conditions, he believes that the results can only be attributed to a pulmonary vasodilatation. In the absence of definite controls of right and left auricular pressures, his conclusions must be accepted guardedly.

In conclusion, the demonstration of reflex vasomotor effects on the pulmonary circulation must continue to be regarded as probable rather than quite certain and the part they play in the regulation of the pulmonary blood flow is left for further investigations.

THE CHEMICAL REGULATION OF THE PULMONARY VESSELS

Numerous researches have indicated that the caliber of the systemic vessels can be affected by chemical substances derived from cell metabolism (e.g., CO_2 and lactic acid). The possibility exists that the pulmonary vessels may also be affected by them either through a peripheral or central action. Investigations have been limited largely to the effects produced by asphyxiation. The earlier work is reviewed by Hill (26). Nolf and Plumier (43) and later Plumier (46) showed that both carotid and pulmonary arterial pressures increase during the initial stage of asphyxiation while the left auricular pressure remains unchanged. This they interpreted as evidence of vasoconstriction. They supplemented these experiments by others in which the circulation was limited to the heart and lungs and, failing to obtain a similar elevation of pressure in the pulmonary artery, concluded that CO_2 causes this constriction by central action alone. Erikson (20) in 1907 studied the reaction of asphyxia after the vagus nerves had been cut and atropin administered but found no changes that could not be accounted for by a damming back of blood. Führer and Starling (21), testing the reaction of vessels in the heart-lung preparation, always found the pressures to rise in the pulmonary artery, left and right auricles, indicating that these pressure changes are entirely due to a "back-pressure effect" from the failing left heart. As asphyxia continues, the right heart also dilates and the pressure in the pulmonary artery may then fall. Similar effects were obtained from inhalation of CO_2 when the O_2 supply was maintained adequate. Obviously, the reaction of the pulmonary vessels to chemical products of metabolism requires further experimentation before any definite conclusions may be reached. Convincing experiments that oxygen excess may in any way affect the state of contraction of the pulmonary vessels have not been submitted. Retzlaff (48), interested in explaining the therapeutic benefits of oxygen inhalation, found that the lungs inclosed in a plethysmograph, after the technic of Weber, decreased in volume. This he attributed to an active vasoconstriction which squeezes blood from the lungs. As the pulmonary arterial pressure showed no alteration and the systemic arterial pressure often showed a decline, it required a fanciful explanation on the part of the author to harmonize the results.

THE CARDIAC REGULATION OF THE PULMONARY CIRCULATION

While the nervous and chemical control of the pulmonary vessels undoubtedly plays an important, if not as yet fully understood part in the distribution and flow of blood in the lungs, it is obvious that the total volumes of blood contained in the pulmonary vessels must be governed by the relative discharges of the two sides of the heart. Whenever, therefore, the systolic discharge of the right heart exceeds that of the left—as may conceivably happen either when the systemic venous inflow increases or the systemic arterial resistance is greatly raised—intense pulmonary congestion must inevitably occur unless compensatory mechanisms are set in operation. With the pulmonary volume so intimately dependent on the relative discharges by the two sides of the heart it is wonderful as Henderson and Prince (25) remark "not that pulmonary congestion sometimes occurs but rather that it is not commonly caused." "It is still more remarkable, that a condition of pulmonary depletion. . . . . is unknown either to physiology or to clinical medicine."

It is, therefore, important to analyze the possible compensatory mechanisms which prevent too great a deviation of pulmonary blood volumes from the normal. Henderson and Prince (25) have reported observations which help to explain why excessive pulmonary arterial pressures and intense active congestion are prevented when the systolic discharge of the right heart is augmented. In a heart so perfused that the diastolic volumes and systolic discharge of the two ventricles could be separately studied, they found that the left ventricle has a much greater power of responding to increased venous pressure than the right. By virtue of this mechanism they believe that pulmonary blood volumes are maintained at nearly a constant level, and in the following manner:

> "Whenever any condition increases the volume of blood pumped into the pulmonary vessels by the right heart, the rise of pressure in the pulmonary veins stimulates the left ventricle to larger strokes. So long as the left heart is capable of responding to even a moderate rise of the diastolic distending pressure by relaxations and contractions larger than any of which the right heart is capable, pulmonary congestion is effectively guarded against. In this respect the left heart acts somewhat like a dam of moderate height across the outlet from a reservoir. The pressure and volume can go no higher than its top. It is only when an abnormally great pressure is involved in the distention of the left heart, as the result of injured valves or excessive tonus, that the top of the dam is so far raised as to produce pulmonary congestion. On the other hand, whenever the output of the right heart is in any way considerably decreased, the left ventricle responds to the lower pressure in the pulmonary veins by a more than proportionally decreased stroke. Thus, the lungs are never drained of their blood."

The numerous direct observations as to effects of changing systolic volumes discharged by the right heart or pulmonary pressure lung volumes, etc., already analyzed (page 250) indicate clearly that, if such a mechanism operates in the intact circulation, it is not adequate to prevent pulmonary congestion entirely. Straub (54) in recent experiments found that the initial and maximum pressures in the left ventricle remain unchanged under such conditions, which would indicate a failure of the left heart to react in the manner indicated by Henderson and Prince. Personal observations (76) tend to confirm the idea that in such cases the left ventricle does respond in a compensatory manner to relieve the pulmonary circuit of an excess of blood by virtue of a larger systolic discharge. Contrary to Straub, I have found both initial and maximal pressures to increase promptly in the left ventricle when the systemic venous return increases.

Considering all the evidence, we must conclude that a certain degree of active pulmonary congestion and a definite increase in pulmonary arterial pressure must necessarily follow an augmented systolic discharge of the right ventricle. Indeed, it is not until the pulmonary venous pressure and blood volume are augmented in this way that the initial tension and systolic discharge of the left ventricle increases. Once set into operation, this mechanism tends to prevent pulmonary engorgement from becoming excessive, but it is never able to reduce the pulmonary volumes or pressures back to normal.

Whenever the left ventricle is compelled to expel its blood against a very high arterial resistance, the systolic discharge is less complete. We may examine into the reasons why this does not necessarily produce an intense passive congestion of the pulmonary veins and also a passive increase in the pulmonary arterial pressures. The experiments of Straub (54) led him to postulate the following sequence of events when the left ventricle contracts against augmented arterial resistance:—When the left heart is incapable of expelling its normal quantity of blood, a considerable quantity is accommodated by the diastolic distention of the left ventricle itself. This causes, at once, an increase in initial tension by virtue of which the pressure-maximum is increased and the systolic discharge restored to normal. Aside from a very insignificant increase in pulmonary blood volume, the lung circuits remain entirely unaffected. If the ventricular dilatation becomes so marked that normal volumes can no longer be expelled, pulmonary venous congestion supervenes. Even so, pulmonary arterial pressure may remain unaffected; indeed, Straub's results indicate that

in some cases the maximum pressure in the right ventricle may be reduced. It is not impossible in such cases, as Henderson and Prince (25) suggest, that the interventricular septum may be crowded to the right, thereby diminishing the filling and as a result the systolic discharge of the right heart. In other words, a "back-pressure effect" is prevented by the simultaneous operation of two factors—the improved working capacity of the left ventricle and the mechanical reduction in the discharge of the right.

We may suppose that, whenever "back-pressure effects" do occur—as apparently is frequently the case under experimental conditions reported in the literature (cf. page 256), these compensating mechanisms are not able to entirely prevent the operation of the primary influences tending to prevent intense pulmonary congestion.

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CONTRIBUTIONS OF THE WAR TO THE PHYSIOLOGY OF THE NERVOUS SYSTEM

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It is not essential in this discussion by way of introduction to do more than roughly outline the general methods, during the progress of the recent war, by which contributions to this branch of physiology were achieved. The war created a vast, and yet extremely haphazard experimental laboratory in which lesions of the human central and peripheral nervous systems were inflicted at almost every conceivable point. Such patients as survived formed material for the study of any defects which existed in their nervous mechanism as the result of a lesion, the location of which in a large number of instances was exactly known. In this respect, then, we are dealing with a well-recognized method, which has heretofore been carried out experimentally upon animals, now applied through the agency of war to human beings.

In general, we may divide the injuries of the nervous system into two great classes; first, those due to direct lesions by missiles of war, and secondly, those due to indirect lesions from concussion or shell explosion. This review will deal with the contributions to physiology which were made as a result of the first class of cases. For this purpose the subjects will be taken up under the general headings of *1*, Cerebrum; *2*, Cerebellum; *3*, Spinal Cord; *4*, Peripheral Nerves; and *5*, Sympathetic System.

It may be said at this point, that by far the greatest number and without question the most important contributions to the physiology of the nervous system during and because of the war, were made by French and British writers. There is a fair amount of Italian and German literature on this subject, while the American articles are meager, except in the field of the peripheral nerves. So far as the writer has had access to the German articles, they seem largely confirmatory of the work done in France and England.

CEREBRUM

Regarding the early general symptoms common to almost all head injuries, little need be said. Chatelin (1) has summed these up tersely at the beginning of his book. They consist for the most part in headache and dizziness, to which may be added such disturbances as insomnia, changes in character, defective memory and fatigue after slight mental effort. In a similar manner Dubois (2) has recorded the late symptoms of this generalized type from which so many patients with head wounds suffer, irrespective of the location of the lesion. In addition to the possible presence of all the early symptoms, many other disturbances are likely to appear such as very indefinite sensory troubles, marked asthenia, difficulty in attention, memory fixation, hypermotivity, irritability, instability of pulse, febrile exacerbations, emaciation and even modifications of the cerebro-spinal fluid. Leriche (3) has devoted an article to what he calls the "headache of hypotension" in patients having an old trephine defect in their skulls, while Oppenheim (4) has paid special attention to the amnesia of traumatic origin. A very interesting observation concerning generalized trauma of the cerebrum is that of Foa (5). This writer records a case of fatal hyperthermia, following great compression of the left cerebral hemisphere. Nothing was found at post-mortem to account for the condition. This agrees with certain clinical experiences in the surgery of the brain where, after an operative exploration, usually of the posterior cranial fossa, but sometimes elsewhere, the patient may die within 24 hours with an excessive temperature elevation,—in children sometimes up to 108° or 109° F. In these patients perfect consciousness may be retained up to the very terminal stage.

a. Motor area. This region, already so well recognized, and more carefully worked out than any other separate brain area, was nevertheless made the subject of much further study. One of the first things noted and dwelt upon by authors was the fact that lesions near the precentral gyrus, but not actually involving it, might give a total, but temporary hemiplegia of the opposite side, probably due to the concomitant edema around the wound. Such paralyses, though absolutely complete at first, would almost invariably recover normal function, provided no actual destruction of the Rolandic zone by the missile itself had taken place. No distinctly new data have been recorded relative to the physiology of the motor cortex. Mme. Benisty (6) produced a monograph of careful studies in which she confirmed the previous find-

ings, namely, that the motor zone comprehends *1*, the ascending frontal convolution (precentral gyrus), and *2*, the posterior insertions of the first, second and third frontal convolutions.

b. Sensory area. Concerning the zone of cortex, supposedly having to do with sensory impressions, and now fairly generally conceded to lie in the region posterior to the fissure of Rolando, certain very definite contributions have been offered.

Mme. Benisty, in the work referred to, came to the following conclusions as a result of her studies. She maintained that the sensory zone comprehends the ascending parietal and the superior parietal convolutions, the supramarginal gyrus, the angular gyrus and perhaps the posterior part of the first and second temporal convolutions. The ascending parietal she believed to subserve particularly the limbs, the rest of the parietal lobe to subserve the sensibility of the whole opposite side of the body. Lesions of this latter portion gave general hemihypoesthesia, while lesions of the ascending parietal gave sensory troubles disposed in longitudinal bands occupying the terminal extremities of the limbs. The sensory-motor zone for the hand she believed to have two secondary centers, one for the internal or volar surface, and the other for the external or radial surface. For the foot a single center only could be defined. Orientation in space was dependent upon the integrity of the parietal lobe. Loss of the sense of attitude was especially related to the gyrus supra-marginals.

Roussy and Branche (7) reported some interesting studies which have been confirmed by other writers concerning a syndrome of sensitivity in one hand following a lesion in the cortex of the opposite side of the brain. In both their cases the lesions were small, discrete wounds, limited to the parietal lobe. In these patients the sensory findings were confined to the hand and consisted in tactile anesthesia, painful and thermic hypoesthesia, loss of the sense of position of the fingers, astereognosis and loss of osseous sense. To this syndrome the authors have given the name "La main sensitif corticale." They confirmed the work of Head and Holmes in distinguishing between cortical and thalamic lesions, in so far as the former were characterized by the variability of the results obtained following moments of inattention and lack of judgment, and by the rapid fatigue of the patients.

Guthrie (8) raised the question of a trophic center in the post-central region. This was based on the finding of slight musuclar atrophy following wounds of this area, a short while after their reception. In the months following, the patients were affected with various nutritive troubles.

The most exhaustive study of sensation and the cerebral cortex was made by Henry Head (9) and published in 1918. This work was based upon observations of twenty-one cases of cerebral injury, most of the lesions being superficial, without penetration of the cortex. Many of the patients were officers. The author employed a series of well-defined tests, and took graphic records of each case. These tests included *a*, appreciation of spatial relations, such as passive measured movements, compass test, and localization; *b*, appreciation of graduated response, by the use of tactile hairs, heat and cold and pin prick; and *c*, appreciation of similitudes and differences of weight, form and texture.

The first sign that sensation was affected in consequence of a cortical lesion was a statement by the patient himself that the tests were less easy in the affected hand. The method of investigation showed that the sensory activity of the cortex was not associated with the crude recognition of touch, pain and temperature, but rather endowed sensation with discriminating faculties. These could be divided into three categories, namely, recognition of spatial relations, graduated response to stimuli of different intensity, and appreciation of similarity and difference in external objects brought into contact with the external surface of the body. These three aspects of sensation could be distributed independently of one another in consequence of cortical lesions. The passive movement test and the tactile hair test were the most deficient in cases of cortical lesions. The faculty of recognition of similarity and difference could be distributed and conserved independently. The chief characteristic of cortical lesions was the irregularity of the response.

Subcortical lesions were characterized by the facility of obtaining a threshold, the regularity of the responses, and the different grouping of the dissociated sensibilities. The optic thalamus was apparently the seat of those physical processes which underlie crude sensations of contact,—pain, heat and cold, together with the feeling tone they evoke. Thus the sensory activity of the cortex was found to be essentially discriminative in its nature.

c. Frontal lobes. Up to the present time it has been well known that there is no specific syndrome referable to the function of the frontal convolutions. They have always been assumed to be the abode of the higher functions of mentality and of intellect, but the exact information obtained has often been conflicting and largely based on the finding of tumors in this region, which may have had pressure influences upon other parts of the brain as well. Even after a study of gunshot injuries

limited to the frontal lobes proper, Chatelin concluded as follows: "One can say without exaggeration, that up to the present there is no symptomatology proper of the frontal lobes."

Notwithstanding this authoritative and comprehensive statement, there have been one or two extremely careful studies which ascribe definite clinical syndromes to lesions of this brain area. Marie and Behague (10) described a clinical picture of "disorientation in space" associated with deep frontal lesions. The authors gave detailed observations upon a series of twelve patients. Their tests were controlled by observations upon patients with wounds of the parietal, occipital and other areas, and such patients never made the same mistakes as those wounded deep in the frontal region. There was no question of any cerebellar involvement in any of the cases, and all tests of cerebellar function were normal. In brief, these authors found that patients having isolated, deep wounds of the frontal lobes, either right or left, showed disorientation in space confined to an inability to tell direction. No trouble in telling depth, nor in duration of time was ever noted. The typical case was a man who could not find his way around a room, or several rooms, with which he had become thoroughly familiar. He had to be shown the way back to his room every day if taken out of it. Another patient got lost in a small section of Paris with which he was quite familiar.

Another interesting manifestation of frontal lobe injury was that described by d'Oelnitz and Cornil (11). These authors laid stress upon psychic disturbances of a particular kind—a state of apathy, associated with constant and abnormal gaiety, to which they applied the term "discordant euphoria." In addition they noted many times in cases of frontal lobe abscess, a pupillary myosis on the side of the lesion, and believed this to be quite a characteristic sign of compression of the frontal lobe.

d. Aphasia. By far the most important and perhaps the only thoroughgoing study of the localization of the various speech centers was made by Marie and Foix (12) in 1917. Their contribution was based on a large series of cases which were observed over periods of time ranging in many instances from a few days to six months or a year. They were thus able to compare the acute disturbances with those which remained as permanent, after a sufficient time for maximum recoverability. Their method of projecting the wound of the skull upon the exact portion of underlying brain was according to the scheme of cranio-cerebral topography published by Marie and Bertrand in 1916.

(Compte rendus de la Societe de Neurologie.) By this means an approximation within an error of 5 to 6 mm. was claimed to be possible, as proved by the cases verified at that time.

The authors first divided speech difficulties into two groups, the "syndromes anarthriques" and the "syndromes aphasiques proprement dites." The former applied to the various types of difficulty in speaking itself, from an absolute inability to articulate to the different grades of dysarthria, slowness and scansion of speech. The second group concerned itself with what the writers considered aphasia proper, i.e., loss of vocabulary, comprehension of speech, reading, writing and calculating, and also such allied difficulties as apraxia.

As a preliminary procedure, the whole area of the left hemisphere which, it was found, might be involved in any speech difficulty, was mapped out. In this area two very distinct zones were found to exist, an anterior, concerned with difficulty in speaking itself (syndromes anarthriques) and a posterior, concerned with aphasia proper, (syndromes aphasiques proprement dites). The anterior zone included the inferior portion of the ascending frontal convolution (precentral gyrus) and the adjoining posterior portions of the second and third frontal convolutions. The posterior zone was again subdivided into three parts as follows: *1*, zone of the two upper temporal convolutions; *2*, zone of the supra-marginal gyrus, and *3*, zone of the angular gyrus. Lesions of each of these three zones gave special aphasic syndromes. Between the two main zones (anterior and posterior), there was an area, deep lesions of which gave rise to a total aphasia (aphasia globale), which was anarthria plus aphasia proper.

Concerning the anarthric syndromes, it was found that the brain area involved included not only the inferior portion of the precentral gyrus, and the posterior portions of the two lower frontal convolutions, but deeply inward it involved the insula and the lenticular nucleus. It was impossible to say whether the superficial or deep portions played the principal rôle, but it was evident that the third left frontal convolution did not play an essential part in the function of language.

Lesions of the anarthric area, studied before any recovery had begun to take place, and therefore presumably involving a large portion of the zone, gave rise to the following syndrome: inability to speak at all, or if not absolute inability, speech confined to one or two monosyllables; inability to read even the simplest commands, though if these commands were spoken to the patient they were carried out correctly, thus showing conservation of the comprehension of speech; ability to write,

though very slowly and with difficulty; ability to calculate to slight extent, but not beyond two figures.

Lesions of the anarthric zone, studied after maximum recovery had taken place, the residual lesion therefore presumably confined to a certain small portion of the zone, showed the following:

a. Lesions of the anterior portion of the zone tended to almost complete recovery.

b. Lesions of the posterior portion of the zone gave a residuum of well-marked dysarthria, with slight traces of aphasic symptoms.

c. Lesions of the upper portion of the zone gave a residuum of slowness and scansion of speech, with slow ideation.

Concerning the syndromes of aphasia proper due to lesions of the three subdivisions of the posterior area of speech disturbance, these studies showed the following:

1. Zone of the two upper temporal convolutions. These lesions gave rise to an inability to name objects (anomia). Comprehension of speech, reading, writing and calculating were greatly affected. Intelligence was diminished.

2. Zone of the supra-marginal gyrus. Lesions of this zone gave rise to a general aphasia in which anarthria and aphasia proper were associated. All the elements of speech were affected. There was often a bilateral apraxia.

3. Zone of the angular gyrus. In lesions of this zone there was a predominance of alexia. Ability to write was intact. Comprehension of speech, ability to calculate and to name objects were considerably affected.

The other important study of the aphasias, as a result of war wounds, was that recently published by Henry Head (13) in 1920. Like all the other work of this author, the observations were both extensive and intensive, and the material carefully chosen with a view to the subject in hand. As noted by the author, the soldiers who were victims of wounds during the war formed infinitely superior subjects to those upon whom previous studies of aphasia had been carried out. They were in the best of health when wounded, were extremely interested in the progress of their examinations, willing and anxious to coöperate in every way, thus contrasting strongly with the aphasics seen in civil life who are old people, broken down, and with intellectual capacity diminished. In addition to the choice of material, the author devised some new serial methods of examination, "making it possible to utilize the inconstant answers, characteristic of all cortical lesions."

From his observations Head concluded that, "disorders in the use of language, due to an unilateral lesion of the brain, cannot be classed under the categories of isolated affections of speaking, reading or writing," nor could they be explained "as due to destruction of images, 'visual,' 'auditory' or 'motor.'" The previous termed conditions of "word-blindness," "mind-blindness" and "imperception," "are all associated with more or less disturbance of the power to form images, complicated in some cases" by speech disorders.

In regard to what has been called motor or Broca's aphasia, Head was convinced that this was not solely an anarthria or dysarthria, as urged by Marie, because in such cases careful examination showed that "not only external speech, but certain aspects of internal verbalization are affected."

Under the heading "symbolic thinking and expression," the author grouped together the various types of aphasia and speech disorder, saying that "this name has been chosen because the gravest and most definite disturbance is to be found in the use of words, figures, and other symbols." It was found that the functions comprised under the above term might become dissociated as a result of lesions situated in different parts of the brain, this dissociation being "analogous to the effects produced on sensation by injuries to the cerebral cortex." Two or more aspects of symbolic formulation were affected in most cases of aphasia. Finally, the author comprised under four headings the various dissociated forms of symbolic thinking and expression.

a. Verbal aphasia—"essentially a defect of word formation."

b. Nominal aphasia—"a defective use of names, and want of comprehension of the nominal value of words or other symbols."

c. Syntactical aphasia—Talking jargon, and lack of grammatical coherence.

d. Semantic aphasia—consisting "in a want of recognition of the full significance of words or phrases."

No attempt was made by Head in this article to localize in the brain these various disorders of speech.

e. Visual area. The evidence concerning the function of this brain area has been both abundant and thoroughly convincing. As a result of the work of Holmes, Lister, Marie, Chatelin, Monbrun and a host of other observers it may be said that the exact cortical representation of all areas of the retina has been practically established.

In 1915, Marie and Chatelin (14) contributed a valuable series of observations concerning the cortical visual area in a study of some 31

cases of wounds of the occipital lobes. The site and extent of the lesions was determined as exactly as possible by means of x-ray and craniometric measurements, as well as by the operative findings when these were available. They divided the types of cases observed into three groups.

1. Cases showing a horizontal, inferior hemianopsia. In these patients the lesions were always confined to the superior portions of the visual area, that is, the upper lips of the calcarine fissure, the completeness of the hemianopsia depending upon the extent of the destruction produced. The obvious conclusion was that the upper halves of the retinae were represented in the supra calcarine area.

2. Cases showing inferior, quadrant hemianopsias. Four out of the 5 cases in this group showed defects of the left lower quadrant, with the lesions situated in the right superior lips of the calcarine fissure. The other case, in which there was a right lower quadrantal defect, had a probable lesion in the left upper calcarine lip. These cases presented strong evidence toward the localization of the right and left sides of the upper halves of each retina in the corresponding right and left portions of the superior lip of the calcarine fissure.

3. Cases showing central and paracentral scotomata. There were 11 patients in this group from whom satisfactory conclusions could be drawn. The size of the scotomata varied directly with the extent of the lesion, and the more closely the defects approached the fixation point, the more superficial was the lesion at the extremity of the occipital pole. If the defect in the field of vision was below the horizontal line on one side of the median line, the lesion was found to be situated in the opposite side of the superior and posterior calcarine area. In the two cases in which there were superior paracentral scotomata, they were on the left side of the median line and the lesions were in the right posterior extremities of the lower calcarine lip. The findings in this group, therefore, supported the evidence already given above, and in addition there was strong proof that the macula representation was at the posterior extremities of the occipital lobes at the end of the calcarine fissure. There were a few cases of peripheral scotomata with lesions in the anterior portions of the visual area, making it probable that the peripheral portions of the retinae were represented farther forward. In the cases studied for colors, there was found to be no justification for a cortical center for color vision.

Holmes and Lister (15) reported in 1916 a study of 23 cases of wounds situated in the occipital lobes. The exact location of these lesions was

determined by means of careful craniometric methods, supplemented by x-ray examination and the findings at operation or autopsy. Many painstaking observations of the defects in the fields of vision of each patient were made, both with the ordinary perimeter and with a Bjerrum's screen. The evidence which they advanced toward proof of the cortical representation of vision may be stated briefly.

1. Cases in which the brain injury was located in the calcarine region (area striata), above the level of the fissure, showed loss of vision in the lower half of the visual field, signifying that the corresponding upper portions of the retina were represented in the supra-calcarine area.

2. Cases showing small, central scotomata had lesions confined to the occipital poles, at or about the level of the posterior extremities of the calcarine fissures, with probable damage to the hindermost ends of the area striata only. This offered strong evidence in support of the view that the cortical representation of the macula lay in the posterior extremity of the visual area.

3. Cases showing paracentral scotomata, extending from 10° to 30° from the fixation point, also had lesions at or near the posterior extremity of the calcarine fissure, supporting the above conclusion as to the cortical representation of the macula.

4. Paracentral scotomata limited to the lower quadrants of the visual fields had lesions situated above the posterior end of the calcarine fissure, confirming the conclusion that the upper half of each retina was represented in the dorsal part of the area striata.

5. Paracentral scotomata limited to the upper quadrants of the visual fields had lesions on the under surface of the occipital poles, giving evidence that those portions of the lower quadrants of the retina, in the region of the fovea, were represented in the lower and posterior parts of the area striata.

6. The size of the scotomata varied directly with the depth of the wound from the occipital pole, making it probable that the concentric zones of the retina, from its center outwards, were represented in serial order from behind forwards, in the visual area.

A further very valuable and careful contribution concerning the cortical visual areas was made by Holmes (16) in 1918. The methods of study were practically the same as in his previous paper in collaboration with Lister. In regard to the cortical representation of the retina, Holmes cited four groups of cases.

1. Patients with inferior, paracentral scotomata. The lesions here were confined to the dorsal parts of the visual area, giving defects in the

lower halves of the visual fields on both sides of the median line, confirming the earlier conclusions as to this site for the representation of the upper halves of the retinae.

2. Superior paracentral scotomata. These were found to be much less common. Only 5 such cases had been described in previous literature, and in all, the lesion involved the lower part of the visual area. Holmes added 3 more confirmatory cases, making further proof that the lower halves of the retinae were represented in the inferior calcarine area of the occipital poles.

3. Sector scotomata. Four cases were observed. The cortical damage was located on the exposed mesial surfaces of the area striata. These lesions gave scotomata lying along the vertical radii of the retinal fields. By exclusion, it could possibly be assumed that the retinae on either side of the horizontal radii were projected to the visual cortex which occupies the walls of the calcarine fissure.

4. Peripheral scotoma. The author cited one case in which the probable lesion was confined to the anterior part of the calcarine area. The fields of vision showed an homonymous contraction of the left peripheries, thus offering evidence that the peripheral areas of the retina were represented in the forward portion of the visual cortex. Further confirmation lay in the fact that peripheral vision was never affected by local lesions of the posterior portion of the area striata.

In addition to the occipital lesions, Holmes described one case of deep injury to the right parietal lobe. In this patient the only disturbance was in visual attention. He would only see one hand being moved in his visual field, when in reality two were being moved, one in his right, the other in his left visual field. Such disturbance was believed to be analogous to the "attention loss" in cutaneous sensibility as described by Head and Holmes in 1912.

A report by Monbrun (17) in 1917 confirmed in all respects the observations of Marie and Chatelin and those of Holmes and Lister. He concluded that the optic radiations were divided into two independent bundles, each of which placed the retinal quadrant into relation with the corresponding lip of the calcarine fissure. He agreed also that the cortical center for the macula was localized to the most posterior part of the calcarine area.

It may be said then that there is a general agreement among those who have studied the cortical localization of vision, as to the representation of the retina in the brain areas adjacent to the calcarine fissure, and extending out slightly on to the lateral surface of the tips of

the occipital lobes, the most central portions of the retina being placed farthest posterior, and the peripheral portions being placed more and more anteriorly. Finally, there was no evidence in any of the series of observations to support the older idea of a bilateral representation of the macula.

A contribution by Riddoch (18), also in 1917, was important. Incidental to his main subject, he was able to confirm the work of other writers as to the localization of the visual center. In addition to this, and more especially, he studied the dissociation of visual perceptions following injuries to the occipital lobes. As a result of his observations upon ten wounded officers, he was able to demonstrate that the perceptions of light and movement were the first stimuli to be recognized in a recovering visual field. The field for movement could be recorded on a chart, and offered the earliest indication of recovery. Further, he found that the appreciation of movement and the recognition of an object were always dissociated in patients in whom recovery of vision could be demonstrated, the field for the former, which is the more primitive perception, being the larger. The recovery of the appreciation of movement began at the periphery of the visual field and extended inward toward central vision. He considered these types of visual dissociation analogous to the dissociations of general somatic sense impressions described by Head and his co-workers as occurring from cerebral injuries.

In addition to the results achieved with regard to the cortical representation of the retina, there have been certain other interesting and instructive observations concerning the localization of allied visual phenomena. It is not within the province of this review to go into the great detail which would be necessary to give an adequate idea of the intricate visual processes involved. Suffice it to say that it has been pointed out in papers by Smith and Holmes (19), Riddoch (18), Holmes (16), and Holmes and Horrax (20), that patients who had sustained a bilateral cerebral injury in the neighborhood of the angular gyri, or upper part of the supra-marginal gyri, exhibited certain striking defects in visual association perceptions. These defects included a loss of visual attention and retentiveness, defective spatial orientation and inability to tell the relation of objects in space, and in some instances a partial or complete loss of stereoscopic vision. As these functions are not purely sensational, the lesion causing them should probably be regarded as an interruption of the association paths between the occipital cortex and the rest of the brain.

CEREBELLUM

In 1917 Holmes (21) contributed a notable article dealing with cerebellar functions, in which he differed from certain findings of André-Thomas. In regard to the latter's contention for the existence of "anisosthenia" or loss of tone in certain muscles and relative hypertonicity in their antagonists, Holmes was quite emphatic. This condition was searched for by Holmes in the majority of his patients, but in no instance was he able to confirm André-Thomas' observations by finding that the loss of tone was limited to certain muscles. In all unilateral injuries of the cerebellum the hypotonia was homolateral, involving all the muscles of the affected side, but usually more demonstrable in the upper extremity.

In considering the disturbances of voluntary movement, Holmes was able to show by kymographic records that there were distinct differences on the side affected by a unilateral cerebellar lesion. These consisted in a slowness in the inauguration of simultaneous movements, a slower attainment of the exertion of full power, a delay in commencing relaxation, and a slowness in effecting relaxation. He also showed by the ergograph that the affected side tired more easily than the other.

From these observations his conclusion was that the cerebellum might therefore be regarded as a motor reinforcing organ.

> It seems, however, probable that it takes no direct part in the processes, whether initiated reflexly or voluntarily, that produce motor effects, and that it does not augment these, but that it "sets" or "tunes" or regulates the activity of certain motor mechanisms, most probably spinal, so that the response to a volitional stimulus is immediate, effective, and proportional to the intensity of the cerebral impulse. . . . . In addition . . . . it also exerts an influence on the efficiency of this response, by determining the complete fusion of the elementary muscle twitches.

Concerning the phenomena which have been spoken of generally under the term "cerebellar ataxia," Holmes' observations would indicate that this condition was produced by other factors than atonia, asthenia and astasia. One of the chief of these he has referred to as the "decomposition of movement," analogous to the "asynergia" of Babinski. All these components he believed were due essentially to loss of the ability to start and stop a movement promptly and normally, and not to loss of tone or to faulty action of agonists and antagonists. He concluded that "the cerebellum also exerts a regulating and coördinating influence on the motor centers that effect voluntary movements,

and by this means assures their harmony, precision and correct range." He also attributed nystagmus to the throwing out of this particular regulatory mechanism. In regard to any localization of function in the cerebellum Holmes stated that his observations were inconclusive.

As an adjunct of his pre-war studies, which have already been alluded to, André-Thomas (22) in 1918 published his observations upon three exhaustively detailed cases of wounds of the cerebellum. This work brought confirmation to the studies of Babinski concerning active movements in cerebellar lesions, asynergia, etc. Regarding localization of cerebellar function, the author summed up his own previously published observations, as well as those of others who had written on the subject, notably Van Rynberk, Bolk, Rothman and Barany. His conclusion was that there were centers in the cerebellum, less well defined than in the cerebrum, but nevertheless quite specialized for the arm, leg, trunk, neck, etc., and for the articulations of limbs; centers not only for motor activity, but for regulation of tonus of the agonistic and antagonistic muscles. His conception of the cerebellum as a whole was as a regulator of the action of these agonists and antagonists.

With the exception of the monographs of Holmes and André-Thomas, studies of cerebellar function have been confined to occasional case reports nearly all of which contained merely confirmatory information. One, however, by Leri (23) in 1916 should be noted, as the lesion was found to be absolutely discrete, and the resulting disturbance of function quite definite. The patient received a superficial wound which was shown to be limited to the superior part of the inferior vermis. There was also a slight scratch of the left cerebellar hemisphere which could be completely discounted. The symptoms which followed consisted in a perfect picture of the two syndromes of Duchenne and of Babinski, i.e., titubation, tremor, vertigo, asynergia and adiadochokinesia,—all confined exclusively to the legs. There was no atony, asthenia or dysmetria. The author was led to the conclusion that the center for coördination of movements of the legs lay in the superior part of the inferior vermis cerebelli in man, thus agreeing with the experimental work on animals.

SPINAL CORD

It can be said without hesitation that the work of Head and Riddoch (24), (25) on the physiology of the completely divided spinal cord, as a result of war wounds, stands in a class by itself among con-

tributions to the functions of this portion of the nervous system. Other studies to be mentioned, notably those of Lhermitte, Roussy, Guillain and Barré, and Buzzard, touched on various phases of the combined observations of Head and Riddoch, but not in such an exhaustive manner, nor did the observations extend over as great a length of time.

Both articles by these English writers, that of Head in collaboration with Riddoch, and that by Riddoch alone, appeared in 1917 in the same number of *Brain*, and should be considered together. The first of these papers concerned itself primarily with the reflex activities of the bladder and of the sweating apparatus. The studies were made upon three complete divisions, and five partial but severe lesions of the spinal cord. Complete observations of the changing conditions in the patients were made at frequent intervals over periods up to 336 days after their injuries. It is impossible in a short review to give any adequate idea of the detail of these elaborate studies, but the salient features which seem to have been established beyond question may be collected under the following headings. Direct quotations from the authors are here used freely.

a. The automatic bladder. "When the spinal cord has been completely divided, the bladder may begin to expel its contents automatically as early as twenty-five days after the injury, under favorable conditions." Sepsis may partially or wholly prevent this automatization. "The form assumed by the activity of such an automatic bladder is entirely independent of the site of the lesion in the spinal cord." In serious injury or complete division of the spinal cord above the lumbar region, "automatic evacuation and the complete act of micturition may be facilitated by the most various afferent impulses passing into the lower portion of the spinal cord." Thus, scratching the sole of the foot, thigh or abdomen evoked a flexor spasm accompanied by an emptying of the bladder, even when its contents did not reach one-half the amount otherwise necessary to produce a contraction of the muscular wall. "After the destruction of the lower lumbar and sacral roots, the bladder may act automatically in an identical manner, except that it can no longer be influenced reflexly by any afferent stimulus. When the lesion is confined to the lower end of the spinal cord or to the lower lumbar and sacral nerve roots, the patient may be conscious of tension within his bladder, may recognize the occurrence of contractions in its muscular wall, and may experience that pleasure which normally accompanies evacuation. But these sensations have no effect on the automatic activity of the bladder." Upon an auto-

matically acting bladder, deep breathing was found to act as a stimulus to evacuation.

b. Excessive sweating. Hyperidrosis associated with gross lesions of the spinal cord "represents the activity of the nervous system below the lesion, and further, paroxysmal sweating can be excited by almost any stimulus which sends afferent impulses into the spinal cord below the lesion." Such stimuli consisted in scratching the sole of the foot or the skin of the abdomen, provided they evoked a flexor spasm, while other stimuli such as injection of fluid into the bladder, or into the rectum as in giving an enema, were equally effective.

c. "Mass" reflex. Inasmuch as any afferent stimulus below the level of the lesion in a completely divided spinal cord may evoke a diffuse reflex response, manifested by flexor spasm, evacuation of the bladder and excessive sweating, this response may be spoken of as a "mass" reflex. "When the spinal cord reacts with this massive response, it is obvious that the reflexes have, to a great extent, lost their local signature."

In the article by Riddoch, activities of the bladder, of sweating, and the "mass" reflex were further considered and confirmed, and in addition, the muscle and tendon reflexes were taken up in detail. For these observations five patients with completely divided spinal cords were available, and one incomplete section, some of the cases being the same ones which appeared in the joint paper. The author separated the clinical course of the cases into three stages, the second only of which, namely, that of full reflex activity, is of chief interest physiologically. This stage began from 7 to 21 days after injury. These studies showed that the clinical picture of a total transverse lesion of the spinal cord in man, as hitherto described, was imperfect, inasmuch as the "portion of the spinal cord caudal to the lesion not only recovers its reflex functions, but becomes highly excitable."

The first reflex to appear was that known as "flexor spasm." This was evoked during the stage of reflex activity by nocuous stimulation of the sole of the foot, or of any part of the lower extremity either of the superficial or deep tissues. In its fully developed form it consisted in flexion at the hip with adduction of the thigh, flexion at the knee, dorsiflexion at the ankle, and upgoing toes. "In all patients during this stage, when reflex contractions occur in one physiological group of muscles, simultaneous inhibition of their antagonists can be demonstrated." It was further noted that in obtaining a flexor reflex of one side, a reflex in the opposite limb also occurred, usually flexion. Other

reflexes which could be evoked, involved the abdominal muscles. These consisted in responses ranging from a simple contraction of the external oblique and rectus abdominis, up to a general contraction of the ventral abdominal wall, or a flexor spasm of the abdominal wall plus that of the lower extremities, the stronger the stimulus, the more widespread the reflex. The field of stimulation for producing these reflexes comprised the superficial and deep structures of the abdomen and lower extremities.

Reflexes involving the genital organs were also observed and perhaps can be described best by direct quotation. "During this stage of reflex activity, one of the most receptive fields for exciting reflexes is the genital area. In its full development the reflex from the genital area involved the musculature of the genital organs, of the ventral abdominal wall, and of the lower limbs. The components of this reflex are, in their order of appearance: (a) Cremasteric and dartos reflexes; these are evoked by movements of the prepuce over the glans, by handling the scrotum, by scratching the inner portions of the surfaces of the thighs and of the perineum. (b) Bulbo-cavernosus reflex, which is excited by gently irritating the glans through the prepuce or by pricking the glans penis. (c) Erection of the penis and seminal emission." Knee jerks and ankle jerks were obtained by the usual method of stimulation, but were later in appearance than the reflexes already described. In the cases studied, they appeared earliest on the 21st and latest on the 53rd day after injury. The response at first was a mere tightening of the relaxed tendon, but eventually the ordinary response could be elicited. A few clonic jerks could be obtained at the ankle at times, but never a well-sustained clonus.

Certain features of reflex bladder activity were noted other than those mentioned in the previous article, and reflex defecation was found to take place as well. Each organ was found to respond to a content of fluid injected, which varied in the case of the bladder from 100 to 650 cc., and in the case of the rectum from 56 to 280 cc.

Finally, regarding certain other activities, the following should be quoted. "In the stage of reflex activity the vasomotor balance is more stable, when febrile complications are absent, than in the stage of muscular flaccidity. If the legs are let down gradually little or no edema develops. . . . . Apart from complications, the skin of the paralyzed parts regains a good color and a normal temperature."

As already mentioned, there are certain other observations upon spinal cord injuries to which reference should be made. Early in 1917

Buzzard (26) reported a verified case of total transection of the cord at the level of the fourth dorsal segment. In this patient a reappearance of the knee and ankle jerks was noted as well as involuntary flexor spasms. Plantar stimulation produced homolateral flexion and spasmodic extension of the limbs of the opposite side. Stimulation of the skin of the abdomen caused a contraction of the abdominal muscles while periodic evacuation of the rectum and bladder was observed. The facts are in complete accord with those described in greater detail later by Head and Riddoch.

Guillain and Barré (27) also in 1917 published a series of observations upon 15 cases of total spinal section. Their studies were confined to the more acute stages, and not continued observations over a long period of time. They noted ordinarily a conservation of the cutaneous plantar reflex in flexion, frequent conservation of the cremasteric reflex, and rare conservation of the superficial abdominal reflexes.

In 1918 Roussy and Lhermitte (28) produced a monograph on injuries of the spinal cord. In many aspects it recapitulated the observations of Head and Riddoch as did also a further contribution by Lhermitte (29) in 1919. These authors summed up the previous findings concerning conservation of reflexes after a total transverse section, noting that Dejerine and Mouzon (30) in 1915 had described the appearance of flexion of the legs upon stimulation of the sole of the foot. In addition, they themselves noted automatic, spontaneous movements of flexion and extension, and in one case rhythmic contractions of the abdominal and flank muscles. Two cases of erection for a short period of time were observed. Regarding electrical reactions in the muscles below the level of the lesion, they obtained a greatly diminished response both to faradic and galvanic stimulation.

PERIPHERAL NERVES

The number of published investigations concerning the functions of the peripheral nerves, as studied after gunshot or other injuries during the war, has become so enormous that any proper summary of the situation at the present time is well-nigh baffling. The interest, however, may be said to have centered around a few fundamental considerations. These include the clinical evidences of a return of function in nerves whose continuity has been completely interrupted; the difference in time at which these evidences appear; the sequence of return of the various modalities of sensation; the mechanical and physiologi-

cal factors influencing return of function; and finally the changes in the electrical reactions present in recovering nerves. In addition, there has been some dissension from the previously accepted ideas as to the transmission of the modalities of sensation.

In 1915 Tinel (31) published an article dealing with what he termed the sign of formication (signe da fourmillement) in nerve lesions. The author believed that this was the most important and almost the only early sign that regeneration was occurring in a previously divided nerve. The sign was obtained by pressure or percussion of a nerve trunk below the lesion, such stimulation producing to the patient a sense of "creeping" or formication in the cutaneous territory of the nerve. In the author's words:

> It appears about the fourth to the sixth week. Then it increases progressively, and from week to week one can follow along the course of the nerve, the progression of the formication produced, parallel to the advance of the axis-cylinders; it extends towards the periphery; it reaches the branches of division of the nerve; it ends in the course of several months by attaining the cutaneous territory itself. . . . . It not only permits one to follow the advance of regeneration, but again it furnishes by its rapidity of migration, by its intensity, by the territory in which it manifests itself, precise information as to the quality, extent and limitation of regeneration.

In a later monograph in 1917, Tinel (32) took up in detail the clinical syndromes of interruption, compression, irritation and regeneration of peripheral nerves, but aside from the sign of formication, nothing of new physiological interest was added. In regard to the electrical reactions in regenerating nerves, this author regarded them as "variable in different cases and difficult to interpret." In his observations the R. D. did not become modified until after the appearance of axis cylinders, and of muscle tonus.

In 1917 also, Mme. Benisty (33) published a book dealing with her own observations upon the regeneration of nerves, as well as summarizing the accepted views of other workers on this subject. She believed that in the main most of the observations confirmed the pre-war work of Head and Rivers. In contradistinction to Tinel, this author gave as the earliest sign of recovery the elicitation of pain when the skin was pinched within the sensory area of the injured nerve, as noted by André-Thomas and Belenki. This pain on pinching, ill-localized and persistent, was found to be referred to small circumscribed spots, just as the paresthetic zones were later for pricking and heat. These zones gradually spread and coalesced. (A. Thomas.) Formication was said to be

the next sensation to return, and after that, pain in the muscles whose nerve supply was given off highest from the injured nerve. After this she believed that the return of sensation was as determined by Head and Rivers.

Benisty devoted considerable study to the electrical reactions obtained in both degenerating and regenerating nerves, and the muscles supplied by them. Her conclusions were based largely on the observations published in collaboration with Marie in 1915. The subject is a complicated one, and by many observers including Tinel deemed too inexact and variable from which to draw positive data. The views of Marie and Benisty, however, were evolved from a most painstaking study of a large series of cases, and may be briefly summarized.

In serious lesions due to wounds, the injured nerve and muscles supplied by it were inexcitable on faradic stimulation. There were galvanic inexcitability of the nerve, often with considerable hypoexcitability of the muscles, sluggishness of contractility, polar reversal for certain muscles and equalization or normal polar formula for other muscles. Longitudinal excitability from the first few weeks onwards after injury exceeded the reaction obtained at the motor points. There was no galvanic hyperexcitability of muscles in patients wounded at least 6 weeks previously, either when total anatomical sections existed or where interruption was of a physiological nature of long standing. In patients upon whom nerve suture was done, a return of faradic contractility was noted from the 3rd week to the 4th month after operation. Also in many of these patients voluntary motility was noted to be restored to a considerable extent even when electrical contractility and especially faradic excitability still remained in abeyance. But in many cases faradic contractility reappeared, partly at any rate, several weeks or months before voluntary motility occurred. Faradic excitability of nerves did not always reëstablish itself before faradic excitability of muscle. The conclusion was that faradic contractility could appear in muscles before voluntary motility.

Faradic recovery takes place slowly but progresses methodically up to the time when voluntary motion appears, and occasionally it diminishes or disappears for a short time when voluntary motility is about to return. On the contrary, in many cases, especially in complete sections which have been sutured, voluntary motility returns before electrical contractility, and during the first few weeks or months which follow the onset of motor recovery, it is possible to find faradic inexcitability or even galvanic inexcitability of muscular masses which have been previously affected by paralysis and complete R.D. The electric current is rapidly diffused into the normal muscles of the neighborhood.

The appearance of faradic excitability in paralyzed muscles was a promising sign, no matter how slight. "This return generally coincides with the signs of sensory recovery, and an arrest in the amyotrophy."

Another important communication concerning especially the return of function in recovering nerves, was that of Burrow and Carter (34) in 1918. The observations were made upon a series of 1000 cases. These authors stated that trophic and vasomotor functions were the first to recover, and that next came deep sensibility, usually in the order of sense-pressure, perception of movement in joints, roughness and pressure pain. Radiating and ill-localized sensations referred to wide areas, and usually associated with tingling, appeared next, and conformed to the protopathic sensations of Head and Rivers. After these came the accurate perception of light touch, while lastly and very imperfectly appeared the discriminating sensations, such as the stereognostic sense.

A study of 875 cases by Price, Feiss and Terhune (35) in 1919 emphasized certain important factors in securing the recovery of nerves, especially the necessity of early repair by excision and suture of the divided ends. They held also that volitional effort played a part in the return of function. In regard to individual nerves they found that the musculo-spiral and sciatic made the best recoveries.

An interesting communication was made by Mingazzini and Fumarola (36) in the same year. These writers did not confirm the previous widely accepted studies of Stöffel and others concerning the distribution of different bundles of fibers to certain groups of muscles or sensory areas. They stated that no matter where a nerve was injured, certain groups of muscles had a predilection to be paralyzed,—notably the muscles most distal in a limb. In the arm the muscles of the hand were the ones nearly always paralyzed, no matter where the median, ulnar or musculo-spiral were injured, while in the leg the external popliteal fibers tended to suffer, no matter what part of the sciatic was traumatized.

Concerning certain sensory changes and other aspects of regenerating nerves, Grimberg (37) published observations also in 1919. He found that hypoesthesia and hypoalgesia were always present after complete nerve division, and comprised a zone about the area of total sensory loss. On the other hand, a hypoesthetic area was not always hypoalgesic, and vice versa. He stated that in the syndrome of complete interruption, areas of hyperesthesia and hyperalgesia were never encountered. Apropos of regeneration, this author observed that the

first sensory signs returned as early as thirty days after injury or suture, and that the musculo-spiral and ulnar regenerated earlier than any other nerves, while the first sign in the sciatic appeared as early as 2 months after operation. The second phase of regeneration he regarded as the reduction of the anesthetic and hypoesthetic areas, and with the reduction of analgesia, appeared patches of hyperalgesia. These became more marked until anesthesia and analgesia entirely disappeared. He regarded Tinel's sign of formication as of only corroborative value, as it was found to be present in cases of complete division with no regeneration.

A study of the various forms of sensation in peripheral nerve lesions was made by Cobb (38) in 1919 on a series of 540 cases. He brought evidence, from the previous work of Trotter and Davies, 1913, and of Boring (39), 1916, to show that the transmission of sensation by separate systems, i.e., the "epicritic" and "protopathic" hypothesis of Head, was certainly questionable. Cobb's own studies corroborated the work of Boring, Trotter and Davies, inasmuch as he found that dissociation of the various modalities of sensation occurred only when comparing stimuli qualitatively different and quantitatively unequivalent.

Another careful study, also in 1919, of a different phase of sensation, was that of Pollock (40). This author was interested especially in the overlap in sensory supply after nerve lesions. He showed from his studies that the area of prick pain supplied exclusively by an individual nerve was far less than the accepted sensory distribution of that nerve. He called the area between the border of exclusive supply of prick pain, and the border of its accepted sensory supply, the "area of algesic nerve overlap." When nerves serving adjacent areas were severed, prick pain between these areas was not present, nor did it return before the sense of touch. When the algesic overlap area was sensitive after section of a nerve, and this region was adjacent to another nerve area, if the second nerve was then severed, a complete analgesia resulted in the previous sensitive region. Further, when prick pain was present in an area of possible overlap, or returned on to the sensory distribution of a severed nerve, subsequent section and resuture of this nerve did not change the general extent of the sensitive area, i.e., the pain sense, returned or present before the operation, was not due to partial regeneration. From these observations the author concluded that the laws governing the assumption of function by nerves adjacent to a severed nerve were unknown. Evidence of this assump-

tion of function was not present immediately after injury, but gradually showed itself at a later date. His studies also apparently showed that the early return of prick pain, before that of touch, was not due to a temporal dissociation of epicritic and protopathic sensation, but to the assumption of function by adjacent overlapping nerves. He stated that the return of sensation to prick pain could be used clinically for the determination of nerve regeneration only when it was accompanied by the return of tactile sense, or when it occurred outside the area of possible overlap of adjacent nerves.

Two other important communications dealing with the peripheral nerves, although largely surgical in their nature, have at the same time certain physiological interests. Stookey (41) in 1916, in common with the majority of later writers, found that divided nerves tended to regenerate better by a mere approximation of their ends, rather than by any process of tubulization, even if such approximation necessitated transference or transplantation of a nerve from its original bed in order to bring the ends together better. He also stated that motor return was earlier the nearer the lesion was to the periphery.

In 1920 Stopford (42) offered a number of general factors which he found had considerable influence on nerve recoverability. In regard to the lapse of time before doing a nerve suture, he found that a delay of more than 18 months gave poor results in distal sutures, but was not so important in proximal ones. Better functional return occurred the nearer the site of the suture was to the spinal cord. Ligature of the main artery in the proximal part of the limb was a factor militating against regeneration. The intrinsic muscles of the hand and all muscles in the distal part of a limb recovered less frequently than the proximal muscles. The author gave as reasons for this the greater distance of the young nerve fibers from their trophic centers, the smaller size of the nerve supply, and possibly the phylogenetic history of the muscles, the smaller, distal ones being the more highly specialized and therefore the less apt to have their nerve supply return. This author also emphasized the advantage over other methods, of careful approximation of the divided nerve ends in doing sutures and advocated liberal resection of the injured ends.

SYMPATHETIC SYSTEM

The outstanding studies during the war on the rôle of the sympathetic, were those of Leriche (43). In 1917 he described his results after interrupting the sympathetic pathway in arteries of the limbs, by decorticat-

ing the vessels for a distance of 8 to 10 cm. Two distinct reactions followed such procedures, the first, lasting for 6 to 12 hours, consisted in a contraction of the artery to one-quarter of its former volume over the decorticated area, feeble or imperceptible pulse in the extremity, and a lowering of the surface temperature of the limb. The secondary reaction, lasting for 2 weeks to a month, consisted in an elevation of 2 to 3 degrees of the surface temperature of the limb, a rise of arterial pressure, and an augmentation and amplitude of the oscillations of "Pachon." During the course of this more prolonged secondary reaction, certain other clinical physiological results were observed. An immediate amelioration of certain "reflex contractures" in the extremities was apparent, and the same applied to trophic conditions of the skin and nails. Another observation was the disappearance of profuse sudations of the hand, from which the author concluded that the function of the sympathetic as the excito-secretory nerve of sweat was established. Of even greater clinical interest was the observation that certain extremely rebellious cases of causalgia, upon which no effect had been produced by division of the nerve in question, were at least temporarily cured by excising the sympathetic from the blood vessel below the lesion, apparently showing that the lesion was not one of the nerve itself, but of the neighboring perivascular sympathetic.

Further studies concerning the origin of the pain in causalgia were made by Tinel (44) also in 1917. He believed it to be essentially a sympathetic symptom, and maintained that it was constituted by a real sympathetic reflex arc, painful centripetal excitation and centrifugal reactions of vasomotor form, secretory and trophic, which helped to keep up and increase the pain. He said that the point of departure of the painful sympathetic excitation might be found in the nerve lesion itself, when the nerve contained sympathetic fibers, and in these cases section of the nerve above the lesion would cure the pain. In the cases where the causalgia persisted in spite of section of the nerves above, it must be that the painful excitation had as its point of departure, the irritation of the sympathetic terminations in the peripheral territory of the nerve, by the intermediary disturbances which determined its neuritis. In these cases, the painful sympathetic excitations, like the reflex responses, were conducted by the lateral paths, probably perivascular. Under the influence of these painful excitations there was established in the sympathetic centers a real state of erethema, of marked hyperexcitability, which diffused into the neighboring centers and even into the homologous centers of the opposite side. This state

of erethema made itself known by "synesthesalgia" which often limited itself to a territory more or less extensive, a real "causalgic field." There were determined, in a quite large sympathetic field, modifications of sensibility, especially a superficial hypoesthesia by inhibition or even blocking of the sympathetic. It might manifest itself at a distance in the causalgic field by diffuse sympathetic reactions, such as profuse sweating, mydriasis and vasodilatation.

In 1918 Girou (45) added confirmatory evidence as to the sympathetic origin of causalgia. He maintained that the dominating findings in painful affections of the limbs were contractures, and in such conditions he found constantly lesions of the periarterial sympathetic. There was alleviation after periarterial sympathectomy.

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THE HEAT-REGULATING MECHANISM OF THE BODY

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WATER AND HEAT: Equalization of temperature in living organisms is best attained through the presence of a mobile constituent which can circulate freely and rapidly. Water above all other liquids is fitted for temperature equalization and regulation; for as Lawrence Henderson (60) points out, it ranks very high as regards three qualities—specific heat, heat of evaporation, and conductivity. The first favors storage of heat; the second permits of very rapid elimination when necessary, as when environmental temperature exceeds that of the body; the third allows rapid equalization of heat within the fixed tissues of the body, minimizing the possibility of injury from local overheating within or without.

The recognition of water as the central factor in the regulation of bodily heat may lend coherence to the following review of some of the many-sided investigations of the past decade.

HEAT REGULATION IN THE LOWER ANIMALS: Even among amphibians and reptiles is seen an attempt to resist the temperature of the environment. For instance, in lizards, while the body temperature is a function of the external temperature, Martin (109) found at medium environmental temperatures (10–35°C.) a tendency toward a carbon dioxid production which is relatively constant. Both above and below these temperature limits the influence of the environment was more marked, with approximation of the van't Hoff law. (Applications of this law to physiological processes are reviewed by Kanitz (79).) Krogh (87) finds neither van't Hoff's nor Arrhenius' formula exactly applicable to metabolism curves. In the frog the nervous influences which produce tone begin to make themselves felt at 20°C., for the rise in metabolism which appears normally at this temperature when the frog is subjected to gradual heating Krogh finds less marked in narcosis.

Martin classes the Australian ant-eater (echidna) as a warm-blooded animal for while the production of heat is directly proportional to the difference in temperature between animal and environment, its body

temperature only varies 10°C. within the environmental range of 5–35°C. This indicates that heat loss can be modified although the animal possesses no sweat glands, exhibits no vasomotor adjustment to temperature, and does not increase its respirations at high temperatures.

Marsupials are the lowest mammals capable of "heat polypnea." Pronounced dependence upon the heat-dissipating mechanism begins with the higher mammals, e.g., rabbits and cats, the heat production not being particularly increased until they are submitted to an environment about 25°C. below their own. Polypnea is well developed but the loss of heat by sweating varies much with the species; activity becomes independent of external temperature. The higher mammals have gained their advantages by a great expenditure of energy, for Martin states that approximately 800 calories per kilo would be saved to an animal by allowing its own temperature to fall 1°C. instead of maintaining it by increased heat production. In the carnivora heat regulation is better developed than in the herbivorous forms; rabbits, for example, are dependent chiefly upon vasomotor regulation, not possessing a satisfactory water reserve.

HEAT REGULATION IN MAN: In man the heat-dissipating or "water-shifting" mechanism, known also as the "physical" regulatory mechanism suffices normally for external temperatures as low as 14–15°. With cooling below this point, heat production rises rapidly and shivering movements appear (141). This constitutes the so-called "chemical" regulation against cold. Young confirms the conclusions of other observers that cold does not increase metabolism until shivering is produced. At external temperatures above 30° the intensity of the metabolism also begins to increase in case the body temperature rises.

The basal metabolism. The normal basal metabolism per square meter per hour varies with age; DuBois' chart (99) shows that at birth this is approximately 30, rising in the first 5 years to over 60, from then on falling with some irregularity to just below 40 calories at 20 years, after which it decreases gradually and regularly to about 35 calories at 80 years. DuBois' height-weight formula gives a satisfactory indication of the surface area of the human body. From the prediction tables of Harris and Benedict (57) the metabolism for any adult can be calculated within a very few per cent on the basis of height, weight, age and sex. Armsby (3) obtains similar metabolism figures in man, cattle, horses and pigs. The significance of this metabolism, which is considerably higher than that exhibited by animals with poor heat-regulating mechanism, is summed up by Lusk (99) as follows: "The

organism preserves the tropical temperature of its cells at the expense of a metabolism which is proportional to the skin area of the individual." According to Benedict what determines the basal metabolism rather than the skin area is "the active mass of protoplasmic tissue."

Diurnal variations in body temperature. The diurnal variation in normal body temperature may be conservatively placed at 1°C. Adjustment to inversion of the daily routine by night workers Benedict (17) found incomplete even after a period of years. In travelling halfway round the world, Gibson (48) found that the diurnal variations maintained a parallelism with the daylight. Goldstein (50) describes as an "interference" curve the diurnal temperature curve of bakers and night nurses. Upon returning to day work the normal curve returns in a few days. But in birds, as shown by Hilden and Stenbaeck (66), the diurnal curve of body temperature can be readily inverted by reversing the habits of life; owls and other night species exhibit maximum temperature in the night.

Influence of age. Imperfections in heat regulation are observed in the extremes of life. Benedict and Talbot (20) have shown that the average rectal temperature and heat production are decidedly subnormal during the first 3 or 4 days after birth. In old age Munk (121) has shown that shivering sets in under conditions in which the "physical" regulation would suffice for younger persons. In doves, Loer (97) finds the average body temperature highest at 2 to 8 months.

Temperature topography. Benedict and Slack (19) concluded that a rise or fall in rectal temperature is accompanied by a similar rise or fall in temperature of all other parts of the body, aside from the skin. Moro (119) has shown that the temperature will exhibit the greatest increase in the axilla or rectum in children according to whether arms or legs respectively have been active. As a result of marching with a heavy load, rectal temperatures up to 39°C. were found by Lippmann (96). The temperature changes were regarded largely as local hyperthermias due to marked muscular activity of the lower extremities.

Hirsch, Mueller and Rolly (71) claimed that the liver is always the warmest part of the body whether during refrigeration, overheating or infectious fever, or after "heat puncture." The temperature increase of muscles after heat puncture was still noticed in the presence of curare but with or without this drug it was said to lag behind that of the liver.

Magne (103) states, on the other hand, that during refrigeration hepatic and intestinal temperatures rise parallel to that of the aorta,

while the muscles show a much greater rise; or with more extreme degrees of refrigeration the muscle curves show less fall in temperature than the other curves. This he associates with the augmented activity of the muscles in regulating against cold. Lefèvre (91) maintains, however, that liver and muscle temperatures run parallel during refrigeration, and ascribes to the liver 30 per cent and to the muscles 40 per cent of thermogenesis; but Magne attributes to the muscles 70 to 80 per cent.

The "surface temperature" of the body is much less uniform than is generally supposed. Benedict, Miles and Johnson (18) find that the temperature of the skin even with well-clothed individuals exhibits differences of 4° to 5°C. in various localities.

As an insulator the efficiency of the human skin varies according to the predominance of fat, corium, or epidermis (157). The epidermis has the poorest heat conductivity, heat passing through fat and through corium respectively two and three times as readily. Variations in the fluid content of its capillaries naturally alters the conductivity of the living skin.

The heat conductivity of the cranium appears to be relatively good. Leyton and Sherrington (94) found that in a chimpanzee with a cranial vault about the thickness of the average human, the application of local cold (ice bag) or heat over the parietal scalp rapidly affected the temperature of a thermometer bulb lying under the dura against the cerebral surface, directly beneath the region of thermal application.

Average body temperature. Precise determination of the average temperature of the body appears at present impossible. Barr and DuBois (16) have, however, devised a differential method by which changes in average body temperature may be determined in a calorimeter. For a given interval they determine the difference between the number of calories produced and the number eliminated. This difference, when divided by the thermal equivalent, affords the gain or loss in average body temperature. For example, heat production, 100 calories, minus heat elimination, 60 calories = heat stored, 40 calories. In a 70 kilo man, the thermal equivalent = 58.1. The average temperature gain is therefore $\frac{40}{58.1} = 0.66°$.

Regulation against cooling: *Chemical regulation.* In animals with well-developed physical regulation chemical regulation only appears as the external temperature descends below 14–15°C. But many instances may be cited (99) in which external temperatures of

20° and 25° are no longer borne by animals without an increase in metabolism, after removal of the protecting cover of hair or feathers.

Rubner (135) showed further the difference made by a protecting layer of adipose tissue; the same dog when thin has a much higher metabolism at various temperatures than when fat. For example, at 15° when thin he produced 109 calories per kilo as against 83 calories when fat.

The older writers, Rubner (135) for example, having contended that shivering movements were not essential to chemical regulation, Sjoestroem (142) investigated three subjects with and without clothes, in a Tigerstedt respiration chamber, maintained at external temperatures varying from 10 to 32°C. He concluded that the increase in oxidations during shivering movements was directly dependent upon the intensity of the movements; these tremors are instigated reflexly through the cold nerves. Without shivering movements the variations in carbon dioxid output bore no relation to the external temperature. While this makes chemical regulation and shivering appear inseparable it must be remembered that heat production even in muscle can occur without external manifestation (68). Exact studies of heat production in heart and smooth muscle are described by Snyder (143).

In extreme refrigeration such as lowers the body temperature, chemical regulation must break down rapidly, for Storm Van Leewuen (147) has shown that cooling tends to reduce the reflex irritability of the spinal cord. This reduction becomes very marked at a body temperature of 26° which may explain why this temperature approximates the lowest compatible with life.

Chemical regulation is largely but not entirely abolished by curare, for Mansfeld and Lukács (107) showed that the heat production falls 10 to 15 per cent after severing the sciatic nerves of a curarized dog. The regulatory influences which are not abolished by curare are said to take their course through the sympathetic nerves, for when the latter are cut sciatic section in the curarized dog no longer reduces the metabolism.

The influence of cooling upon metabolism is illustrated by the experiments of Lusk (99), who compared the heat production after giving glucose dissolved in cold water and in water at the body temperature to a dog placed in a calorimeter. When warm water was ingested the computed heat increase agreed with that actually found, but when cold water was given there was increased oxidation as shown by indirect calorimetry, in order to provide for the heat lost to the fluid in the stomach.

The studies of Lusk upon the influence of cold baths show that heat production may increase by as much as 81 per cent of the normal. (Schapals (137) has described an increase of 176 per cent in the oxygen consumption.) The material first burned is sugar, for the respiratory quotient gradually sinks. In the case of the chemical regulation of the waking hedgehog, however, Henriques (61), contrary to other authors, finds the extra heat produced apparently at the expense of fat and not of carbohydrate; the respiratory quotient remains at about 7.

According to Mansfeld and Pap (107 a) the blood of cooled rabbits can augment the sugar consumption of the heart.

Physical regulation. Down to environmental temperatures of about 15°C. apparently the so-called physical regulation suffices to maintain a fairly constant body temperature. The stimulus is from without (38). By means of this physical regulation the blood, as the most superficial observation shows, is driven away from the surface of the body. It has been customary to assume that this was due simply to a redistribution of the blood, for example, the internal organs increase rapidly in volume as well as in temperature under these conditions. (The various effects of cold baths are reviewed by Matthes (110).) It has been noted, however, that hemoglobin, red-blood cell count and viscosity increase under the influence of a cold environment. Decrease in blood coagulation time has also been described by Velden (152). Under our present conceptions such acute changes must be attributed to alterations in the fluid concentration of the blood.

The effects of cold baths on "brain volume" as determined by the cranial plethysmograph are to cause an increase. How much of this is due to an increase of the cranial blood supply (120), (148), how much to increase in the cerebro-spinal fluid, or how much to actual taking up of water by the nerve tissue has not been determined.

These cranial volume effects are evidently associated primarily with increases in blood pressure as shown for example by L. Hill (69), but I have found in dogs that the cranial volume may continue to increase during the return of blood pressure to normal. Since this increase in brain volume is associated with a loss of fluid from the blood the possibility exists of gradual imbibition by the nervous tissue.

REGULATION AGAINST OVERHEATING: The danger of overheating, as pointed out by L. Fredericq (38), usually arises from within the body rather than from the environment, which affords the excessive cold stimuli. In this connection it is interesting to note that Ruffini's corpuscles, the temperature sense nerve endings for heat, are situated in

the deeper layers of the skin, as pointed out by Ebbecke (32), in contradistinction to the cold sense nerve endings (Krause's bulbs) which lie at the junction of the epidermis and the cutis vera.

It is probable, however, that application of heat either to the skin or to the base of the brain yields similar results (see below).

Filehne (35) has apparently shown that for the initiation of the processes which regulate against overheating no rise in blood temperature is necessary. For in a bath up to the neck at 41 to 42°C., sweating of the forehead began prior to any change in rectal temperature; plunging a hand into cold water stopped this sweating at once.

Chemical regulation. Cessation of the chemical heat regulation is seen in the transition from shivering temperatures to higher ones. When the external temperature is raised from 26 to 37°C. heat production in rats, as shown by A. M. Hill, (67), is reduced by but one-quarter of the amount which it is reduced when the temperature is raised from 15 to 26°. It is difficult to prove that the heat production is reduced as a measure against overheating in an individual who is quite inactive before the heat stimulus is applied. Barbour and Prince (13) succeeded in reducing the CO_2 output of rabbits by heating the basal nuclei and offered evidence indicating that diminished metabolism is one of the factors reponsible for the temperature fall. At high temperatures Lapicque (89) showed that the metabolism of birds is reducible only to a certain minimum. Hot baths, according to Schapals (137), appear to increase heat production by 22.5 per cent. The increased heat production in these instances is of course attributable to the rise in body temperature and has nothing to do with the chemical regulation.

According to Mansfeld and Pap (107 a) the blood of heated rabbits can reduce sugar consumption by the heart.

Physical regulation. This defense against overheating involves evaporation of water from the lungs and skin as well as direct radiation and conduction of heat from the surface of the body.

Both evaporation and radiation are favored by an increased blood flow through the skin. According to the older views vasomotor shifts of blood to the surface at the expense of the interior were chiefly responsible for the increased surface blood flow, but it now appears that the value of these shifts may be much enhanced by augmented blood volume, brought about by rapid dilution (6). The water thus made available serves in the evaporation and radiation processes.

That the peripheral flow is increased in warm environments was shown in the case of the arm by Hewlett, Van Zwaluwenburg and Marshall (63). Stewart has demonstrated the same fact for the blood flow through the feet by the use of his limb calorimeter.

The vasomotor shifts which bring more blood to the surface have been extensively studied, for example, by Mueller and Veiel (120), who indicate the volume changes in the limbs, abdominal organs and brain, under the influence of hot and cold environments, by the following scheme:

STIMULI	BRAIN	ABDOMINAL ORGANS	LIMBS AND SURFACE
Cold	+	+	−
Heat	−	−	+

Strassburger's (148) experiments in which the brain volume was also studied show similar effects of cold and heat, although in the latter case the diminution in brain volume is sometimes preceded by a temporary increase. The rôle of the blood pressure is but a temporary one, as shown by L. Hill (69). The origin of the fluid which dilates the peripheral vessels is by no means definitely determined. Obviously there is loss of fluid from the abdominal organs and from the brain region. (The muscles require further study.) In my own experiments on dogs showing that external heat diminishes the percentage of total blood solids, the volume of the brain became simultaneously diminished.

The conception of an augmented blood volume as the response to external heat accords with many of the older observations on blood cell content and hemoglobin. (Consult Matthes (110).)

Light upon the heat-regulating mechanism from this angle is shed by the recent work of Kestner and his collaborators upon the effects of exercise. They have shown that marked exertion with sweating dilutes the blood, as indicated by diminished hemoglobin content and red blood cell count. Gross and Kestner (52) showed further that this stream of fluid into the blood is associated with an increased rather than a decreased protein content.

Quite recently Cohn, (27) as well as Eckert, (33) has published results indicating that this protein-salt-solution which flows out of the tissues (apparently the muscles are the important stores) is not the result of muscular exertion; for the phenomena are absent when the muscles are tetanized in animals, and in man when the climatic condi-

tions under which the exercise is carried out are such that sweating does not occur. Furthermore sweating procedures such as electric-light heat baths in the entire absence of muscular activity do produce this flow of protein-salt-solution from the tissues into the blood.

The conclusion is that this dilution of the blood is a response to stimulation by heat. Whether the sweating mechanism is the one that is primarily set into action through the temperature-sense nerve endings and the central nervous system, and the water thus lost from the blood replaced by a fluid-regulating mechanism of some sort which overcompensates, or whether the heat directly affects this fluid-regulating mechanism without first drawing off water through the sweat glands has not been determined.

The temporary decrease in white blood cells under the influence of dry heat described by Murphy and Sturm (122) may be another expression of blood dilution.

Under some conditions fluid may be drawn into the blood and then lost by excretion without any dilution of the blood being detected. This is indicated in the experiments of Young, Breinl, Harris and Osborn (161), who found under tropical conditions of heating associated with a considerable rise of body temperature, that the blood (as determined by hemoglobin tests) became somewhat concentrated.

Conditions of overheating, brought about by raising the temperature of the environment, result in a 50 per cent diminution of the flow of gastric secretion excited by sham feeding with Liebig's meat extract (36). It does not appear in these experiments whether the blood was concentrated or diluted at the time of inhibited gastric secretion.

As regards regulation by evaporation of water from the surfaces of the body Soderstrom and DuBois (144) found that in normal men, age 20 to 50, the average secretion of water through the skin and air passages is 29 grams per hour; 24 per cent of the heat produced is thus lost. In boys and old men the amount is a little more.

Osborne (127) has shown that the expired air is probably saturated with moisture under all conditions. The heat output by the lungs can only vary with changes in their ventilation; heat polypnea will be referred to later on.

Galeotti and Macri (44) have shown that the insensible perspiration averages 0.12 gram per square decimeter per hour on the anterior region of the forearm of normal persons at 23°C. While it is claimed that this may become totally inhibited when the temperature of the environment is considerably reduced, it of course becomes increased by heating.

Montuori (116) finds that overheating cats seems to diminish the osmotic pressure of the blood, thus favoring sweat secretion; this may be inhibited by injection of hypertonic NaCl. He claims that lowering of the osmotic tension is an added stimulus to the nerve centers which control sweat secretion. The secretory factor in sweating is emphasized by Kittsteiner (83), who states that the sweat glands in the human arm produce a very marked secretion pressure, often over 25 cm. of mercury,—much higher than the local blood pressure under the conditions.

Before leaving the question of increased blood flow in warm environments it may be pointed out that with very high environmental temperatures it would be of advantage to have a diminished blood flow through the skin rather than an increased blood flow, thus protecting the body to a certain extent in a manner precisely similar to that in which it is protected against excessive cold. Put in another way, increased surface blood flow promotes poikilothermia because it facilitates the conduction of heat either to or from the body. In this connection Berti (22) has shown that very high temperature may produce vasoconstriction; under conditions of extremely high temperature there is also a tendency to increase the coagulability of the blood, the greater viscosity probably hindering the flow through the surface (152).

Climate and heat regulation. The value of evaporation of water from the surface of the body as a method of absorbing heat in environmental temperatures above 37 or 38°C. is illustrated by the work of Haldane (54) and in numerous observations upon heat stroke. The climatic factors most concerned are temperature, humidity and wind rate.

The loss of heat by evaporation, calculated by L. Hill's katathermometer, is taken as the difference between the heat lost in a given time by the wet bulb and dry bulb respectively. Under varying conditions Winslow (156) has shown that the changes in this instrument are an approximate index of bodily comfort. This appears to be another way of stating that they indicate the extent of the strain being put upon the heat-regulating mechanism.

Comfort and health, according to E. H. Hunt (72), can readily be obtained in dry heat where for long periods the air temperature is above that of the body. Of course this requires copious water drinking, sometimes up to 6 liters per diem, but man is provided apparently with a large reserve of water (stored mainly in the muscle), and so readily available that the percentage of the water in the blood is not appreciably diminished even when several liters have been lost by

sweating. Hunt warns against undue or needless use of the stored water under tropical conditions, in cases where the intake is restricted, because if the reserves are extensively drawn on replacement seems to require many hours.

Murschhauser and Hidding (124) showed the effects of environmental moisture upon heat production in a number of series of guinea pigs. In a dry environment increasing the temperature from 21 to 35° reduced the CO_2 production by 18 per cent. When saturated air was breathed, however, CO_2 production was increased by 6.1 per cent under the same conditions. In the first case chemical regulation was found necessary at 21° on account of the dry moving air. In the case of moist air actual overheating of the body took place at 35° because of the inability to give off heat by evaporation.

Lee and Scott (90) found that muscles taken from cats which had been exposed for 6 hours to a temperature of 33°C., with average humidity of 90 per cent, exhibited only 76 per cent of the efficiency shown by muscles taken from animals exposed to a temperature of 21°C. with 52 per cent humidity. Muscular efficiency therefore shows a certain parallelism with the need for heat production.

Young (160) found in white men a high metabolism during the hot season in tropical Australia. The increased heat production was attributed to the ordinary activities of life which had preceded the experiment and which in the hot, moist weather, produce a greater increase in body temperature than in the cool season. (See also Aron (4).)

On the other hand, de Almeida (2) believes that the usual 39 calories per square meter per hour are not produced in the minimal basal metabolism of native white men in the tropics. He finds the heat production averaging from 29.5 to 31.5 calories and attributes this to an adaptation of the heat-regulating mechanism to the lessened need for heat.

Other details relating to climatic effects upon heat regulation are set forth in an interesting fashion by Lusk (99).

Effects of uncompensated overheating. When the regulation against overheating fails and the body temperature rises to any considerable extent, there results an increased metabolism (137), (123). Upon this would depend the tendency to acidosis which has frequently been described by the older investigators and apparently confirmed by the finding of Hill and Flack (70) that the alveolar CO_2 tension is reduced, sometimes almost to 3 volumes per cent. But Haggard (53) finds this

reduction unaccompanied by compensatory changes in the CO_2-combining power of the blood. Hence he assumes that the C_H is lowered. Haggard's experiments were performed on himself in baths giving oral temperatures above 40°C.

Koizumi (84) describes acidosis in thermic fever.

Talbert (149) finds that the sweat resulting from overheating is more acid than that due to muscular activity. The acidity of the urine is also increased. Kittsteiner (83) has shown that heating a portion of the skin increases the percentage of nitrogen and sodium chloride of the sweat there secreted. High (as well as subnormal) body temperatures are unfavorable to certain syntheses such as the formation of ethereal sulphates and of glycuronates, as shown by Hiizu (65).

Many of the physiological effects of overheating the body are described by Heymans (64), who varied the body temperature by heating or cooling an artificial carotid-jugular anastomosis.

Fatal termination of overheating an organism is due to the accumulation of acid, according to Mayer (111), who has shown this to be true for lower forms of life such as corals, anemones, etc. Those forms having the highest CO_2 output and therefore the greatest accumulation of acid in the tissues are the most sensitive to heat.

NERVOUS CONTROL OF HEAT REGULATION: Undoubtedly temperature regulation is intimately interwoven with the balance of other physiological factors, such as the blood content of water, colloids, various ions and metabolites, red and white cells, etc. Many of these factors, however, probably maintain a high degree of constancy in animals which are poikilothermic. Temperature regulation therefore depends on something further. It occurs in fact only in those species which have a highly developed nervous system.

The existence of a thermostat-like nervous mechanism at the base of the brain is indicated by the demonstration that warming of the region of the corpus striatum in rabbits reduces the rectal temperature, while cooling has the opposite effect (6). The vasomotor mechanism of the ears was studied particularly in this connection; warming of this region causes dilatation while cooling causes constriction.

The anatomical region subjected to the temperature stimuli in these experiments was selected because it has given the best results in the much-discussed "heat-puncture" experiments.

Kahn (78) had shown that warming the carotid blood in dogs results in manifestations of increased heat output, namely, peripheral vasodilatation and increased secretion from the sweat pads in the feet.

Similar effects have been demonstrated by Moorhouse (118). The brain therefore shares with the temperature sense nerves a sensitivity to thermal stimuli.

Barbour and Prince (13), in further experiments on the warming and cooling of the heat centers, showed that the carbon dioxid output varied in the same direction as the temperature changes. O'Connor (126) has since brought forward experiments showing, according to his interpretation, that shivering in cats and rabbits placed in baths at various temperatures, depends rather on the temperature of the brain than on that of the skin. For example, when the bath was being warmed up, one animal ceased shivering at 29.6° rectal temperature, the brain temperature having been brought up to 31° by warming the carotid vessels. But later the same animal continued to shiver until the rectal temperature was as high as 34° as long as the brain was kept cooler than 31.2°. The significance which this author attaches to the skin temperature is the determination of the "extra oxygen" consumed during shivering; this is said to be proportional to the extent to which the skin temperature is exceeded by that of the brain.

The effects upon the rectal temperature of warming and cooling the corpus striatum in rabbits have been confirmed by many observers, for example, by Moore (117) as well as Hashimoto (58). In both cats and rabbits the same effects have been described by Prince and Hahn (131). Observers who have failed to demonstrate them have neglected certain precautions such, for example, as the omission of anesthetics. Further demonstration of the significance of the base of the brain in heat regulation is seen in experiments with fever and with drugs, which will be referred to below.

Hashimoto (58) has found in rabbits that the effects of thermal stimuli upon the brain can be augmented by making a second puncture on the opposite side. But if heat is the stimulus through one side and cold through the other, the stimulus on the left side seems always to prevail. Under such circumstances one ear is hot and the other cold. It is suggested that the left "heat center" is the most strongly developed, like the speech center in man.

Decerebration experiments. Further evidence of the importance of the brain for heat regulation is seen in its failure when the entire cerebrum or certain of its parts have been removed. The extent of the decerebration operation necessary to produce poikilothermic rabbits has been defined with a fair degree of exactness by Isenschmid and Krehl (74). They found in a series of animals that the power to resist

environmental temperatures fails suddenly when the transection is located at a point just anterior to the center of the optic thalamus. Similarly Citrone and Leschke (26) have described in the same location a "mid-brain" puncture by which the connections of the brain which are of importance for heat regulation are severed from the periphery.

Rogers (132) has shown that the power of heat regulation is lost in decerebrate pigeons when the optic thalamus has been injured. In such experiments as these it has been shown not only that the animals fail to regulate against changes in environmental temperature but also fail to respond to many drugs and infectious agents. For example, Barbour and Deming (8) have demonstrated a reversal of antipyrine action in decerebrate rabbits. This was confirmed by Isenschmid (73), who has extended the work to include the effects of salicylates and other drugs. Increased heat production can be thus elicited in the absence of central inhibition.

Experiments on cord section. The importance of the central nervous system to heat regulation is well demonstrated by experiments in which the cord has been severed at various levels. It had been recognized clinically for a great many years that lesions of the spinal cord, particularly in the cervical region, were associated with marked disturbances of heat regulation, but the fact remained unexplained that in some of the cases hyperthermia ensued while others were associated with fall of temperature. Gardiner and Pembrey (45) concluded from clinical study that the general effect of lesions of the spinal cord, barring complications such as infection, was to deprive the patient of heat-regulating power in proportion to the extent of the paralysis. (See also Kennaway and Pembrey (82).) The hyperthermias could then be ascribed to restriction of the heat output by excessive use of blankets, etc.

Freund and Strasmann (43) investigated the "regulation range" of environmental temperature in three series of animals; normals, those with section of the fourth to eighth segment of the cervical cord, and those with section of the dorsal cord. Normal rabbits withstood environmental temperatures of 6 to 31°C. with no essential change in body temperature. Dorsal cord rabbits regulated poorly outside of the limits 18 to 31°. Cervical cord rabbits were, however, practically poikilothermic since in environments varying from 19 to 33° their body temperature showed an equally wide range, varying from 28 to 42°C.

Freund (39) ascribes this marked difference between the effect of the lower cervical and the upper thoracic operation to the severance of sympathetic paths leading to the abdominal viscera. More recently he has shown that by performing in addition to the dorsal cord operation a double vagotomy just below the diaphragm, animals become poikilothermic to essentially the same extent as those with cervical cord section. This is probably due to the severance of sympathetic fibers. If instead, the dorsal cord operation be supplemented either by removal of the stellate ganglion or by section of the eighth cervical and first dorsal roots a similar loss of heat regulation will ensue.

Freund and Grafe (40) have made extensive studies of the metabolism of animals with various cord operations. Dorsal cord section plus double vagotomy was found to increase the total metabolism, and especially the protein loss. In explanation the removal of central inhibitions is suggested. After such an operation infectious agents, including trypanosomes, swine-pest bacilli, or hay infusion, increase neither metabolism nor body temperature. This argues against a toxogenic protein decomposition in infectious fevers.

Hári and Janney (56), however, have failed to find that cord operations increase the total metabolism. They state that metabolism becomes diminished by one-quarter or more by cervical section, while below this no effect is produced except possibly a slight increase.

Hannemann (55) states that in frogs the gaseous exchange is increased by decerebration.

Investigations on the brain. Since Ott's (128) time many have attempted a more accurate localization of anatomical "heat centers." (See Liljestrand and Frumerie (95), also Jacobj and Roemer (75).) The results in general have been inconclusive, although the best results from "heat puncture" have usually resulted when the basal nuclei were involved. The last-mentioned authors regard irritation, distention or hyperemia of the walls of the lateral ventricle as the essential cause of heat puncture hyperthermia. They find that corrosives such as phenol or mercury when introduced into one of the lateral ventricles also produce hyperthermia.

The subthalamic region was successfully punctured by Barbour and Wing (15) in experiments where the needle was passed through the orbital fossa instead of from above and the relation of this to Isenschmid and Krehl's (74) and Citron and Leschke's (26) operations appears to make this point of considerable significance. These facts suggest coördination between heat regulation and the pituitary

gland. Leschke (93), however, ascribes the disturbances in the water balance associated with diabetes insipidus to mid-brain injury rather than to disturbance of the pituitary. (Compare Jungmann's (77) "salt puncture.") Karplus and Kreidl (81) have described at the base of the optic thalami a center for the sympathetic nervous system whence, for example, pupillary dilatation can be obtained by electrical stimulation. This region bears relations therefore both to the vasomotor and fluid-regulating mechanisms of the body.

Furthermore the mid-brain bears a definite relationship to the respiratory center. Garrelon and Langlois (46) as well as Nicolaides and Dontas (125) describe a "polypnea center" in this region. The latter find that if the medulla be separated from the brain heat polypnea cannot occur, although the ordinary respiratory regulation persists.

It is possible that there is some psychic control over heat regulation, for Courtier (29) states that a suggestion of heat is followed within a few minutes by a lowering of the surface temperature, the converse occurring upon a suggestion of cold.

Fraenkel (37) states that heat-regulatory powers are poorly developed in neuropathic children.

Although Moore (117) is probably justified in doubting the infallibility of the old "heat puncture" operation as a means of producing fever the weight of evidence which has now accumulated indicates that the processes essential to heat regulation in mammals are largely coördinated at the base of the brain.

HEAT REGULATION AND THE ENDOCRINE GLANDS: Gautrelet and Thomas (47) pointed out that heat regulation becomes much disturbed by removal of the adrenals. Elias (34) finds "heat puncture" independent of these glands. Freund (39) was able to produce fever in dry-fed rabbits with epinephrin but not in those receiving green fodder. The relation of epinephrin "fever" to the water balance is therefore evident.

Cushing and Goetsch (31) have drawn an analogy between hibernation and hypopituitarism and have suggested that other glands of internal secretion are probably without function during hibernation. As regards the thyroid, this conjecture has recently been confirmed by Adler (1), who observed very marked degenerative histological changes in this gland in hibernating bats and hedgehogs. Furthermore he finds that protein-free thyroid extracts will awaken hibernating hedgehogs, increasing both metabolism and body temperature. Thymus, adrenals and phenyl-ethyl-amine all gave a similar result. Thyroid

extract is similarly effective after antipyrine injections in hibernating hedgehogs, but only partially so after quinine injections.

Mills (115) had shown previously that a warm environment increases the colloid matter of the thyroid gland in normal guinea pigs. This increase is accompanied by a flattening of the epithelial cells.

Karelkin (80) found that thyroidectomized animals regulate poorly, being hypersensitive to external heating and cooling, as well as to pyretics and antipyretics.

Mansfeld (105) has emphasized the relationship between heat regulation and the well-known control of the thyroid over oxidations. The increased protein destruction in fevers has been ascribed by Mansfeld and Ernst (106) to the thyroid.

Loewi and Weselko (98) have found "heat puncture" less effective after thyroidectomy. They state further that after this operation there occurs no increased sugar combustion by the heart such as described by Mansfeld (105) for animals with intact thyroids.

Mansfeld and Pap's (107 a) experiments indicate that the internal secretion of the thyroid controls the increase and decrease of sugar consumption by the heart after cooling and heating respectively.

FEVER: Fever may be defined as any condition of positive heat balance not due solely to food, exercise or environment.

Heat production in fever. Infectious and neurogenic fevers are chiefly attributable to partial failure of the heat-eliminating mechanism in ordinary environments. There is little evidence that increased heat production is primarily at fault; for increases due to feeding, exercise, etc., greatly exceed those seen in fever. In the case of "chills," however, such as those of malaria, (16) heat production is probably of importance, but even here there is no evidence that it precedes the temperature rise. Coleman and DuBois (28) found the same coincident increase of temperature and heat production in typhoid fever. In tuberculosis the metabolism is increased very little above the normal. (McCann and Barr (112) and experiments of the author.) In anaphylactic and other fevers Leschke (93) and others found the high temperature even associated with a diminished heat production.

Porcelli-Titone (130) also found great variation in the heat production in fevers according to the infectious agent used. Under some conditions it was even reduced 20 per cent. There were also wide variations in individual animals.

A toxogenic heat production in fever is denied by Freund and Grafe (40) for they find upon the introduction of infectious agents in poikilo-

thermic animals that with the failure to increase the temperature is associated an unchanged heat production.

The production of infectious fever does not seem to require the presence of glycogen in the liver, which distinguishes it fundamentally from "heat puncture" fevers (133).

Heat elimination in fever. The failure of heat elimination to keep pace with heat production during the temperature rise can be deduced from the fact that the surface of the body becomes paler and the perspiration diminished; furthermore if the blood flow through the periphery be measured, this likewise is found decreased.

Hewlett (62) for example, has shown that the rate of blood flow through the arm becomes much diminished during the onset of fever thus accounting for the tendency against an increase in heat elimination. Stewart (146) also emphasizes the importance of reduced blood flow in fever. The blood is assumed to be sent to help the affected organs. He regards the rise of temperature as a result of the vasoconstriction.

Soderstrom and DuBois (144) found that typhoid patients with a rising temperature have a diminished water output. With falling temperature vaporization affords an abnormally high percentage of the calories eliminated.

Barr and DuBois (16) warn us that the skin temperature (which of course is associated with the flow of blood through the skin) is not necessarily a criterion of the slow or rapid elimination of heat, for it is possible for the sharp bend in the gradient of heat output to occur at some deeper level in the body, where the flow of blood is more rapid. The total amount of heat radiated in a given time to the colder superficial layers of the body and thence to the air could thus be as great as that radiated from a hot skin through which much blood is flowing.

Deficient heat elimination in fever has been emphasized by Balcar, Sansum and Woodyatt (5), who show that by dehydrating a dog with intravenous injections of concentrated dextrose solution, very high temperatures may be produced, attributable to concentration of the blood and lack of water available for giving off heat.

Concentration of the blood is a marked symptom in influenza as shown by Underhill and Ringer (150), who compare this condition to poisoning with lethal war gases. In both cases loss of fluid from the blood prognosticates a temperature rise and a change for the worse, the intravenous introduction of fluids often saving the patient's life.

Parallel to the initial temperature rise in coli fever in dogs, Barbour and Howard (12) have demonstrated a concentration of the blood sim-

ilar to that seen with cold baths. During this concentration Barbour and Freedman (9) observed a marked reduction in the salivary response to pilocarpine. This accords with the reduced gastric secretion in fever noted by Meyer, Cohen and Carlson (114).

Nervous regulation in fever. In fever it is said that the body thermostat is "set at a higher level." A normal temperature becomes apparently interpreted as "cold" by the temperature centers, while one of 40° perhaps feels "neutral." Similarly the skin nerves seem hypersensitive to cold, or hyposensitive to heat, whence the subjective "chill."

This alteration in sensitivity on the part of the nervous apparatus might be attributed to a depressing action of toxins upon the nervous system. In accord with this idea Head and Riddoch (59) note in all febrile conditions a diminished responsiveness of the severed spinal cord. Storm Van Leeuwen (147) finds that 38°C. is the optimum condition for the transmission of reflexes through the cord. They disappear entirely at 42°. Furthermore because of the production of polypnea by a central action Nikolaides and Dontas (125) state that the effect of antipyretics on the heat center is one of stimulation.

Because of the effects of "stimulating" the base of the brain mechanically, electrically, etc., it has been said that the heat centers are "stimulated" in fever. If one explains fever by the dual heat center theory of Hans Meyer (113) one may say that the "cooling center" is depressed while the "heating center" is stimulated. Grafe (51) has attributed fever to the supposed irritating action of the decomposition products of bacteria or of the injured tissues upon the heat centers. By the intracerebral introduction in properly sensitized animals of $\frac{1}{30}$ to $\frac{1}{10}$ the necessary intravenous dose of serum, Hashimoto (58) has produced anaphylactic fever.

That the nervous mechanism is essential to some fevers is shown by the failure of infectious agents to act after mid-brain section (26), (76) and after cord section (40), (142).

Water and salt balance in fever. It has been pertinently objected, however, that some fevers can be produced in the absence of the heat-regulating mechanism, notably the sugar dehydration hyperthermia of Woodyatt (5). This investigator rejects the neurogenic theory of fever and advances the idea that the central fact to which a positive heat balance must be attributed is a deficit of free water in the body. Water regulation he admits, however, may in part be under vasomotor nervous control.

According to Woodyatt, in ordinary febrile diseases the symptom of fever is due to a deficit of free-water resulting from an abnormal tendency on the part of the colloids of the body to bind water. The provocative poison leads to changes which increase the hydration capacities of the cell colloids. With the return to normal body temperature, as for example in the crisis of pneumonia, (136), (101), (100), there is a notable release of water or, more exactly, of salt solution from the tissues.

Evidently anhydremia promotes excessive sparing of heat. Accepting the water balance as the central factor in fever, we are nevertheless obliged to correlate its behavior with that of the nervous heat-regulating mechanism.

In the infectious fevers some such process as the following probably takes place. As the provocative poison reaches the tissues (perhaps the muscles in particular) catabolic changes are initiated which increase the affinity of the tissues for water. This general demand upon the blood for water tends to reduce the blood volume, especially at the expense of the surface blood. The skin immediately becomes cooler, and this arouses the nervous regulation against cold, thus exaggerating the processes of vasoconstriction and hemo-concentration. This continues until the blood becomes warm enough for the nervous centers to interpret the temperature as comfortable or neutral.

Without the brain there is apparently no infectious fever, and unless the water loss from the blood be extreme, as in Woodyatt's (5) sugar dehydration, the nervous mechanism is undoubtedly involved in the production of fever.

In "heat puncture" fevers and the like, the original catabolic processes are in the brain tissue itself. They must result in imbibition, which increases the intracranial pressure. This initiates a vicious circle in which the tendency is toward a continually increasing pressure, for the external cerebral vessels become compressed and the catabolic processes which incite imbibition are augmented by the anemia thus produced (25). Increased intracranial pressure, as Moore (117) points out, seems to incite heat sparing processes and these presumably include the tendency of the tissues to deprive the blood of water.

PHARMACOLOGY OF HEAT REGULATION: *Pyretics.* Chemical agents may produce fever in a variety of different ways. As a general thing, as with infectious fevers, the controlling factor is presumably anhydremia. The fate of the water varies with the different drugs.

Diuretics produce anhydremia, by causing loss of water presumably chiefly through the kidneys. Spiro (145) discusses this in connection with the purines, especially theophyllin, which he finds concentrates the blood. This explains Isenschmid's (73) finding that caffeine increases the body temperature of animals deprived of their heat centers.

Mandel (104) observed that in fever there is often a relationship between the rise in temperature and the appearance of purine bases in the urine. Xanthin and caffeine, in his experiments, both caused febrile temperatures, which could be neutralized by sodium salicylate. Besides caffeine and the other purines, salts, sugars and other diuretics increase the body temperature.

The numerous studies on salt fever in infants, beginning with those of Finkelstein, led to the placing of emphasis on the water balance. Peteri reduced the transitory fever of the new-born by giving fluids by mouth, agreeing with Heim and John in speaking of this as a desiccation fever. (See Balcar, Sansum and Woodyatt (5).)

Rolly and Chrjstiansen (134) state that intravenous injections of 3 per cent but not of normal saline solutions always increase the temperature in rabbits.

Wideroe (154) has obtained varying degrees of fever as a result of injecting different salts and attributes the differences to the individual ions. Sodium appeared to be the least effective of the kations; chlorides and bromides always caused a temperature rise.

Fever-inducing cathartics, among which Berrar (21) studied aloin, promote a loss of water by way of the alimentary canal.

In curarized animals Freund and Schlagintweit (42) found the susceptibility to fever from sodium chloride as well as from aloin retained.

Sympathetic poisons, epinephrin, tyramine, and other amines, especially beta-tetrahydronaphthylamine ("B-tetra") as well as ephedrin, all produce fever. In the case of epinephrin, at least in many species, water is lost from the blood to the liver cells and the lymph circulation as has been shown by Lamson (88).

Cramer (30) attributes B-tetra fever to over stimulation of the "thyroid-adrenal" apparatus and claims that it fails to appear in a cool environment. He likens it to heat-stroke.

Hashimoto (58) found that the fever curve induced by sympathetic poisons or by large amounts of cocaine could not be influenced by heating or cooling the basal nuclei, although after small doses of cocaine

it could be influenced. On the other hand, application of cold as well as of heat to the heat centers was able to exert an influence upon fevers produced either by killed typhoid bacilli or by anaphylaxis or sodium chloride. From these experiments he concluded that the sympathetic and cocaine fevers should be attributed to direct chemical stimulation of the "heating centers" with secondary automatic inhibition of the "cooling centers" of Hans Meyer, while the infectious and salt fevers are an expression of increased irritability of the heat centers. In interpreting such results, one must consider that the failure or success in influencing the fever curve may be after all purely a quantitative matter, dependent on the strength of the opposing influence irrespective of the mechanism.

Isenschmid (73), with B-tetra, increased the gas exchange of rabbits after operative destruction of the heat centers.

In the thermogenic action of cocaine muscular activity is prominent, but I find also that the blood may become very concentrated. Isenschmid states that the thermogenic action of cocaine occurs in the absence of the heat centers.

Adler (1) finds that the hibernating hedgehog, from which the central heat regulating mechanism has been excluded by operation, responds to injection of certain hormones, of epinephrin, and of proteinogenous amines by a considerable increase in body temperature. This increase occurs also in hibernating hedgehogs after paralysis of the sympathetics by ergotoxin. It is also observable after both procedures. The temperature rise under all of these conditions is not as great as when the "heat centers," or the sympathetics are intact.

These effects must probably be explained by the redistribution of water by the sympathetic stimulants. The case is one in which the nervous system contributes to fever but is not essential.

Githens (49) finds that ergotoxin raises the temperature of cats and rabbits. It is effective in the latter after curare but not after decapitation or ether. It is therefore assumed to act through the heat centers. Curiously enough, in rats, mice, and pigeons it depresses the temperature.

Hemolytic fever and the like probably result from the action of decomposition products of the blood cells exerting an influence upon the tissues similar to that produced by the agents of infectious fever. Yamakami (158) has shown that temperature curves due to the injection of distilled water are parallel to those resulting from the injection of hemoglobin, etc.

Bock (23) has noted that the introduction of indifferent particles, such as finely divided paraffin, into the blood stream, increases the body temperature. This may be brought about by some diminution in the blood flow through the periphery. Other pyretic substances include hematoxylin and related compounds (151) and liquid paraffins (138).

Depressants. Drugs which are usually classed as depressants in general reduce the body temperature in all cases where the environmental conditions are normal. This is seen particularly in the case of alcohol and the general anesthetics as well as with morphine. These substances usually favor blood dilution and peripheral dilatation.

The inhibiting influence of morphine upon the fluid-regulating mechanism of the body has been demonstrated by Bogert, Mendel and Underhill (24). This may account for the influence of this depressant in rendering animals poikilothermic.

An example of depression of the chemical regulation by drugs is seen in the work of Magne (103), who showed that shivering movements are inhibited by apomorphine.

Magnesium salts were shown by Schultz (139) to be antipyretic even in subnarcotic doses. Calcium, although it antagonizes magnesium narcosis, seems to enhance the antipyretic action.

Ethylenediamine is also antipyretic in subdepressant doses. Tolerance to this effect is readily acquired (11).

Chlorine in high concentrations behaves like a depressant drug in rendering animals poikolothermic although low concentrations produce hyperthermia at ordinary temperatures (6). The temperature changes produced by the lethal war gases are parallel to the blood concentration; the latter seem to account for the former (150).

Attempts to influence the body temperature by heating and cooling the brain during general anesthesia are usually unsuccessful (58), thus confirming the conjecture that anesthetics inhibit the function of the heat center.

O'Connor (126), however, has increased the blood flow through the limbs of cats anesthetized with chloretone or veronal by heating the brain to a temperature still subnormal, or the skin up to normal body temperature The former experiment might be interpreted as showing hypersensitivity to warmth.

Wideroe (154) showed that during ether narcosis no salt hyperthermia can be produced. These depressants are known to have antidiuretic properties thus favoring an increased water content of

the blood. Since they as a rule increase the blood sugar this fact may be brought into relation with their antipyretic action, as will appear below.

Antipyretics. Substances which reduce the temperature in febrile and similar states but not in normal conditions unless the dosage be excessive are termed antipyretics.

Acetyl-salicylic acid in doses reducing fever temperature by 1°C. increased heat elimination in my series of cases by 38 per cent. Similarly, a decrease in elimination was observed during the return to fever temperature. The heat production was but little altered. Antipyretics therefore act chiefly upon the heat-dissipating mechanism. Barbour and Herrmann (10) have contributed evidence bearing on the mechanism of the increase in heat elimination. Salicylates, antipyrine and quinine, in dogs under normal conditions, tend to increase slightly the body temperature and blood solids. In coli fever these drugs dilute the blood, thus accounting for the fall in temperature. All these substances increase the blood sugar which (by osmosis) may account for the blood dilution in febrile cases, in which the water reserve of the tissues is increased at the expense of the blood.

Antipyretics inhibit adrenalin glycosuria, but Mansfeld and Purjesz (108) have shown that this is a renal effect; thus an antidiuretic effect favoring increased blood sugar and blood volume is obtained.

Dextrose, intravenously given, as shown by Barbour and Howard (12), resembles the antipyretics in that it reduces the temperature in fever, causing the blood to become more dilute than under normal conditions. This supports the contention that blood sugar plays a rôle in antipyretic action. Barbour and Baretz (7) found that acacia similarly tends to dilute the blood in fever and to reduce the temperature, which it does not do in normal animals.

Wiechowski (155) showed that antipyrine and similar substances relax the brain vessels in fever but not in normal animals.

Notwithstanding the central action of antipyretic drugs Yamamoto (159) noted no appreciable difference in the amounts of salicylic acid and acetyl-salicylic acid present in brain tissue in rabbits, although the latter drug is much more powerful than the former.

According to Piccini (129) antipyrine, phenacetine and acetanilid all diminish the total oxygen of the arterial blood.

Hashimoto (58) noted certain differences between antipyrine and salicylates on the one hand and quinine on the other. The antipyretic effect of the former could be increased by the heat stimulus to the

basal nuclei or could be completely counteracted by the cold stimulus within half an hour. On the other hand, during quinine action the heat and cold applications were both quite ineffective. He interprets this as a confirmation of the old idea that the quinine effect is not brought about through the heat centers but through direct metabolic inhibition. This, however, could be equally well interpreted as showing that quinine has a depressant action upon the brain similar to that exhibited by the anesthetics. Hashimoto himself demonstrated such an action in the case of morphine.

He finds further that convulsive and medulla poisons (picrotoxin, santonin, veratrin, and digitalin) reduce body temperature and subsequent heating the centers may produce a still further fall, but cooling produces no rise. These results lead him to conjecture that such poisons do not depress the "heating center" directly, but stimulate the antagonistic parasympathetic "cool centers" (said to reside in the medulla) primarily and directly. Camphor, of which the point of attack as a convulsive poison lies in the cerebrum, behaves like an antipyretic in that cooling and heating of the centers is able to affect the camphor temperature fall, whence it is concluded that the antipyretic effect of camphor like that of antipyrine is through the "heating centers" and not as with picrotoxin in the "cooling centers."

Krauss (86) has shown that the antipyretic effect of nitrites is greater after "heat puncture" than in normal animals.

Magyary-Kossa (102) has pointed out the antipyretic effect of carbon dioxid (by inhalation or asphyxial procedures). It is seen in normal as well as in febrile conditions.

HEAT REGULATION AND CARBOHYDRATE METABOLISM: When the environmental temperature is varied Freund and Marchand (41) as well as Silberstein (140) have described corresponding changes in the blood sugar content which becomes less with heat and greater with cold. These effects might be attributed partly to dilution and concentration respectively of the blood.

Kramer and Coffin (85) found hyperglycemia in dogs exposed to cold for a day or more although not for briefer periods; Lee and Scott noticed that the blood sugar of animals which have been exposed to environments of 33°C. with average humidity of 90 per cent is only 94 per cent of the normal amount.

As described by Lepine (92), while extreme refrigeration causes the blood sugar to increase and then disappear, reduction of an animal's temperature only to, say 36°C., gives a more lasting hyperglycemia.

According to Freund and Marchand (41) an environment sufficiently warm to raise a rabbit's own temperature will also give hyperglycemia. They observed the lowest blood sugar content at environmental temperatures between 30° and 34°C. But nervous control of temperature is independent of the blood sugar for heat regulation was found intact in phloridzinized dogs.

In fevers Lepine (92) has investigated the blood sugar content and usually finds it little altered. In cases where there is hyperglycemia he attributes it to an irritating effect of fever toxins upon the fourth ventricle. Freund and Marchand (41) showed fairly constantly an increase in the blood sugar content in fever but this was of such a degree as may well be accounted for by blood concentration.

The effect of dextrose administration or injection upon the body temperature appears to depend largely upon whether it results in diluting or concentrating the blood. During the stage of dilution it certainly acts as an antipyretic in fever (12). When however it produces marked dehydration it raises the temperature (5).

Fever and antipyretics exert little effect upon the respiratory quotient.

BODY TEMPERATURE IS REGULATED BY WATER-SHIFTING, BUT UNDER NERVE CONTROL: As the organism finds itself in an increasingly favorable environment it inclines toward an attitude of outspread relaxation; but upon the approach of unfavorable conditions a tendency to assume a spherical form is seen. These facts are well illustrated in single cell organisms. Their purposefulness is obvious when the unfavorable condition happens to be temperature.

Of the two extremes of temperature man's chief enemy is the cold, and must become more so with the passing of time if the physical fate of the world be correctly predicted. Besides the voluntary assumption of a drawn-together position to protect against cold, the water reserve of the body is withdrawn from the surface to the better insulated parts. With warm environments however the water is not only brought to but poured freely over the surface of the outspread body.

In general the higher the development of the animal the greater becomes the capacity for dissipation of heat, while the mechanism for saving or dispersing it becomes correspondingly more complex, as is seen for example in the water-shifting rôle of the nervous system.

The shock of cold is akin to that of the emotions, asphyxia, etc., hence Cannon's (25) ideas concerning the nerve-adrenal complex may be applied to the heat regulating mechanism; for the shock of cold will undoubtedly discharge epinephrin into the blood, blanch the skin and

drive water out of the circulation. (Lamson's (88) epinephrin polycythemia.)

Whether or not the adrenal secretion is of significance, the part played by the nervous system is essential.

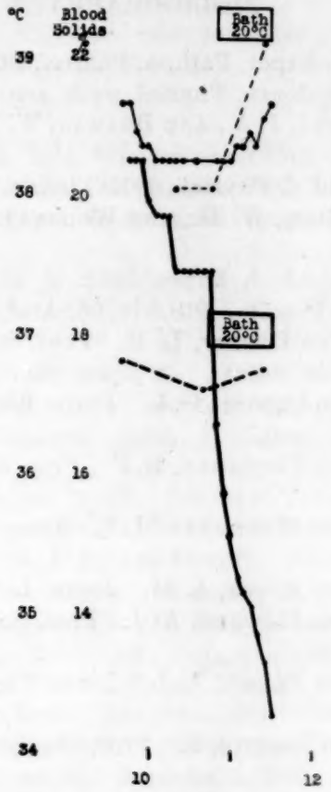

Fig. 1. Effects of cool (20°C.) bath upon dog with and without nervous heat regulation. Upper two curves, normal dog; lower two curves, dog after section of sixth cervical cord segment; continuous lines, temperature; broken lines, blood solids.

Note that normal dog keeps temperature from falling by means of blood concentration. Cord section dog is poikilothermic because blood concentrating mechanism is broken down.

This mechanism is illustrated by experiments I have recently performed with E. Tolstoi (14). In the accompanying figure the upper two curves illustrate the behavior of a normal dog in a cool bath (20°C.). The body temperature (continuous line) is maintained,—even raised slightly; this is accomplished by blood concentration (the broken line represents the blood solids). In the two lower curves are seen the behavior under the same treatment of a dog with spinal cord severed

at the sixth cervical segment. The body temperature falls steeply *because the blood fails to become concentrated.* The connection between the temperature sense nerve endings and the water shifting mechanism has been severed.

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